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Methods for Characterising Patient–Specific Corneal Biomechanics

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Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

Robert Frost
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Summary

This thesis addresses the problem of generating a patient-specific numerical model of the human cornea, using its patient-specific geometry and mechanical properties. We propose several methods to reconstruct the patient-specific geometry of the cornea in an automatic fashion, as well as different protocols to determine patient-specific material properties of the corneal tissue under different loading conditions. Ocular healthcare has become rapidly important during the last decade, supported by the increment of safety in surgical procedures, and the reduction of associated costs. However, over or under corrections after refractive surgeries are still causing a certain degree of visual impairment, patient dissatisfaction, and an increment of costs due to secondary surgeries. Furthermore, concern about the underlying biomechanical sources of ectatic diseases, such as Keratoconus, has encouraged the search for a better definition of the mechanical properties of the ocular tissues. In this vein, non-contact tonometers (NCTs), or air-puff devices, have become a reference in Ophthalmology to perform intrasurgical assessment, or to provide an insight into the mechanical properties of the corneal tissue in pathological and healthy eyes.

Throughout the course of this dissertation, our contribution to the field of Corneal Biomechanics is presented in different milestones. First, we carry out a theoretical in silico study to better understand the physical grounds of NCTs, the role of different ocular features (intraocular pressure, material stiffness, and geometry), and what these clinical tests really characterize. Second, we develop a novel automatic methodology to reconstruct patient-specific corneal geometries where data is available (provided by commercial topographers), allowing to simulate a general air-puff test. Third, we propose different mathematical techniques to predict patient-specific material properties of the cornea based on clinical biomarkers (maximum displacement in a NCT, intraocular pressure, and corneal geometry), showing the capabilities of numerical methods in helping to assess in clinics. Fourth, we propose a novel numerical-experimental protocol so as to determine the mechanical properties of the corneal tissue using inflation and bending tests. In this way, we try to avoid an ill-posed material optimization by minimizing both stress states simultaneously. Fifth, using the information provided by our patient-specific material protocols, we simulate patient-specific Astigmatic Keratotomy surgeries in animal models (New Zealand Rabbit). To ensure that equivalent optical metrics are used when comparing experimental and numerical data, we have developed, and validated using commercial software, an in-house ray tracing algorithm. Thus, a consistent validation and optimization procedures are carried out. Sixth, as NCTs involve the coupling between fluids (air and humors) and a structure (eyeball), fluid-structure interaction (FSI) simulations are applied to improve NCTs’ simulations, including more realistic load transfers and boundary conditions. Additionally, we study whether FSI simulations are mandatory or under what hypothesis they can be accurately substituted by pure mechanical dynamic simulations.

Keywords: Corneal biomechanics, non-contact tonometer, patient-specific, geometry, material, optics, optimization, finite element, fluid-structure interaction, ray-tracing.
A mi familia,

El futuro pertenece a quiénes creen en la belleza de sus sueños
Introduction

The present thesis has its grounds in the field of Biomechanics, endeavoring to integrate mechanical postulations with numerical methods so as to be relevant in Ophthalmology. This introductory chapter provides an overview of the impact of the ocular healthcare on our society, a basic anatomical description, a brief travel through those ophthalmic devices of interest for our purpose (namely topographers, and non-contact tonometers), and a quick review of the state-of-the-art regarding computational models with application to Ocular Healthcare. Finally, the project framework and the funding within which the thesis is embedded is outlined to gently lead the reader to the understanding of the global motivation of this work.

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1.1 Healthcare Impact on Society

About 90% of incoming information reaches the brain through the eyes. Accordingly to World Health Organization (WHO), about 285 million people are visually impaired worldwide. From these, 39 millions are blind and 246 million have low vision (severe or moderate visual impaired). Globally, the first cause of visual impairment is Uncorrected Refractive Error (URE): Myopia, Hyperopia, Astigmatism, and age-related Presbyopia represent 43% of the total (not including presbyopia). Cataract, with 33%, and glaucoma, with 2%, are the second and third leading causes of visual impairment.¹ Regarding URE, the prevalence of myopia is increasing dramatically among children, particularly in urban areas of South-East Asia. Worldwide, Approximately 800 million people are blind, severely visually impaired, or have near vision sight loss, and 145 million people have low vision due to URE (according to the International Agency for the Prevention of Blindness).² Refractive errors in the Western Europe and USA affect one third of people over 40 years.

Nowadays, refractive surgeries are applied to change the curvature of the corneal surface, and to modify its optical power. Despite the surgical breakthroughs over the last decades (radial keratotomy, RK, photorefractive keratotomy, PRK, and laser in-situ keratomileusis LASIK), the unpredictability of the surgical outcomes remain. This unpredictability is manifested in side effects that can lead to unexpected results in visual acuity after intervention. Sometimes, undercorrection (≈ 11.9%), or overcorrection (≈ 4.2%), may occur and a second “enhancement” procedure is required. In many cases, additional surgery may be used to refine the result. According to the Food and Drug Administration (FDA), close to one million of LASIK procedures are performed annually in U.S. positioning it as one of the most common surgeries. Not only that, but forecasts for 2020 predict an increment of 757,000 and 718,000 LASIK surgeries in Europe and U.S. respectively. However, approximately 70,000 cases did not achieve a visual acuity better than 20/40.³ In 2003, the Medical Defense Union (MDU), the largest insurer for doctors in the United Kingdom, reported an increment of a 166% in claims involving laser eye surgery during the last six years.⁴ Besides, a study reported that around 1% of the laser surgeries develop post-surgical complications.⁵ Not only that, nearly the 18% of treated patients, and the 12% of treated eyes needed re-treatment. Meaning an increment of two or, even, three times the initial costs of the surgery. Especially in patients that developed a post-surgical ectasia, as the secondary treatment requires of collagen cross-linking (with riboflavin method), and intracorneal rings implantation. In 2007, clinical trials carried out by the FDA demonstrated an alarming number of patients experiencing post-LASIK complications (e.g. dry eyes). Besides, the FDA published a review gathering outcomes for the LASIK clinical trials, revealing that about 19% of patients suffered from loss of vision acuity 6 months after the

¹ World Health Organization, Visual Impairment and Blindness; Fact Sheet No. 282 (WHO link to digital version)

² VISION 2020: The Right to Sight Blindness and Vision Impairment Global Facts (VISION 2020 link to digital version); Brian Holden Vision Institute, Global Eye Care Needs (Brian Holden Vision Institute link to digital version)

³ Eye Surgery Education Council, established by the American Society for Cataract and Refractive Surgery. Lasik. (Eye Surgery Education link to digital version)

⁴ BBC news: Laser eye surgery complaints up (BBC news link to digital version)

⁵ Hersh et al. 2003
surgery. In 2010, the prevalence of refractive errors in the U.S. was 26% (according to the WHO), and the prevalence of myopia was as high as 70-90%. Besides, uncorrected refractive errors are the second leading case of blindness, demonstrating that regular eye exams, glasses or contact lenses or refractive surgery could transform the lives of millions of people.

Hence, laser surgery results are not always successful. The FDA website on LASIK states, ‘Before undergoing a refractive procedure, you should carefully weigh the risks and benefits based on your own personal value system, and try to avoid being influenced by friends that have had the procedure or doctors encouraging you to do so’. Some examples of failed LASIK surgeries are,

- Keratoconus can be caused by a laser based refractive surgery, providing that some hidden corneal disease existed previously. In 2015, a prevalence of up to a 2.8% of post-LASIK ectasias was reported. Recently in 2016, more than 160,000 cases of ectasias after refractive surgeries were reported, almost equaling the incidence of keratoconus which is overpassing 170,000 cases. So it can be suggested that post-surgical ectasia is already epidemic.

- Due to a visual undercorrection (i.e. less dioptres than expected are corrected), some patients need to be retreated to improve the surgical outcomes.

- Some patients describe symptoms like ‘starbursts’, ‘ghosting’, ‘halos’, or other post-operative drawbacks, which are thought to be related with the laser technique. One reason could be that the most usual laser based surgeries (LASIK and PRK) may induce spherical aberration (i.e. if the laser undercorrect as it moves outward from the center of the treatment zone, especially when major corrections are made). Other feasible theory proposes that higher order aberrations were present preoperatively, and they increase significantly as a consequence of the laser treatment.

Regarding ectatic disorders, Keratoconus (KTC) shows the major incidence in the general population (1 to 430/2000), but official statistics does not include those who have been misdiagnosed, or lately diagnosed. KTC has a great negative impact on patient’s life since it decreases the visual acuity, and has a lasting negative impact on all aspects of patient’s life. Keratoconus affects three million patients worldwide, with a higher prevalence amongst females. Also, South Asian ethnicity with an incidence probability of 4.4 times higher than Caucasians, and also more prone to be affected earlier. Not only that, but advanced keratoconus can cause ‘corneal blindness’, which is responsible of 40.000 people need a corneal transplant in Europe every year.
1.2 Anatomy

Human eye is composed of different structures and layers (see in Figure 1.1). Among the most important macroscopic structures, those providing the eyeball’s shape are the cornea (i.e. outermost transparent layer), sclera (i.e. white layer protecting and shaping the eye), and limbus (i.e. transition between cornea and sclera). Besides, the cornea, which represents $\approx 45$ of the 60 dioptres of the optical power of a relaxed eye, along with the crystalline, ciliary muscles, retina, and optical nerve are the optical elements in charge of the vision quality. Generally, ocular structures present three main layers: the fibrous layer which protects and gives the shape (tunica externa bulbi), the vascular layer which perfuses the organ (tunica vasculosa bulbi), and the nervous layer which provides with the sensorial faculties (tunica interna bulbi). The mechanical compliance of human eye is mainly characterized by collagen fibrils embedded in the fibrous layer (cornea, sclera, limbus, and lamina cribosa). Although human eye dimensions vary significantly between patients, average measures can be set (see in Figure D.5, Appendix D). Generally, the main dimensions of an emmetropic eye (non-refractive errors) are,

- an axial (sagittal) diameter of 24-25 mm (i.e. distance between the corneal apex and sclera),
- a transversal (i.e. nasal-temporal plane) diameter of 23.5 mm,
- a vertical (i.e. superior-inferior plane) diameter of 23 mm,
- a mean corneal diameter of 11-12 mm,
- an increasing thickness from the center to the periphery (550 to 750 $\mu$m),
- a volume of $\approx 6$ cm$^3$,
- and a weight of $\approx 7.5$ grams.

Finally, the eye is inserted in the ocular socket, surrounded by fat tissue, hold by the extraocular muscles and the optical nerve, and protected from external agents by the lids and eyelids. To preserve the shape, the eyeball is filled with the aqueous humor (anterior chamber) and vitreous humor (posterior chamber), and is subjected to a typical intraocular pressure (IOP) ranging between 12 and 22 mmHg (higher IOP values, $>$22, are considered as incipient glaucoma).

Tissue-speaking, cornea is a highly porous tissue formed by a laminar structure. Apart from the high water content (around 80%), there are three main layers: the epithelium, the endothelium, and the central stroma (see in Figure 1.2.a). Apart from this main layers, there are specialized extracellular structures called Bowman and Descemet membranes.$^{18}$ The constitution of each layer is vastly different. However, the most important is the stroma, which represents the 90% of

$^{18}$ Seiler et al. 1992, Sancho 2010
the corneal thickness. Its structure presents several overlapping collagen lamellae composed of bundles of collagen fibrils (see in Figure 1.2.b-c) surrounded by a gelatinous matrix mostly composed of glycoproteins. The microstructure of the stroma is highly heterogeneous, depending on the specific region and corneal layer being evaluated. The anterior stromal lamellae are more closely packed and less hydrated than the posterior stroma, with stronger junctions between collagen lamellae. Thus, the anterior stroma is suggested to hold a main role in maintaining the corneal strength and curvature. This anisotropy in the stromal architecture is also suggested to result in an anisotropic mechanical behavior of the corneal tissue, being supported by experimental and clinical studies. Furthermore, collagen fibers are differently distributed over surface and thickness. This leads to a complex behavior, exhibiting different zone-wise mechanical (no time dependent), and dynamical (time dependent) properties.

Hence, human cornea follows the typical features of soft biological materials: is a viscoelastic tissue with nonlinear elastic behavior. Due to this, their response against a force is not only dependent on the magnitude of the force, but also on the velocity of their application. As a viscoelastic element, two main properties can be identified in corneal tissue: static resistance, or elasticity, and viscous resistance, or damping. The first property describes the proportionality between the magnitude of tissue deformation and the applied force. The second property represents the dependence on time of the relationship between deformation and applied force.
These properties describing the viscoelasticity of the cornea are in relation with its biomechanical behavior.\(^ {21}\)

### 1.3 Corneal Biomechanics: Experimental Tests, Simulation, and Clinical Devices

Generally speaking, an eye, including or not refractive errors such as myopia, can be considered as healthy when its curvature is parabolic (the rest of anatomic parameters are contained in Appendix D), its thickness is regular and greater than 500 microns, and its collagen structure does not present damage (see Figure 1.3 left). Apart from this ideal situation, singularities are found when ocular pathologies, surgeries, or induced pathologies derived from complications after the surgeries are regarded.

Damage in the collagen net results in a corneal tissue weakening and, as a consequence, a critical change on corneal curvature. The resulting cone-like corneal protrusion (see Figure 1.3 right) is known as ectasia, and its origin can be genetic or human-related. When the origin is genetic, the disease is known as Keratoconus, a non-inflammatory ectatic disease in which the collagen fibres lose their organization.\(^ {22}\) When the origin is human-related, generally induced by a refractive surgery (e.g. LASIK\(^ {23}\)), it is called post-surgical ectasia (e.g. post-LASIK ectasia). In the beginning, the eye presents a planar region over the corneal center due to the ablation of the corneal tissue during the surgery (see Figure 1.3 center). However, since a resistant part of the stroma is taken out, a mechanical weakness is induced and the corneal tissue bulges out.

Therefore, anatomical and geometric characterization of the corneal structure and anterior segment has become a crucial analysis in Ophthalmology and Optometry.

**Clinical Tests**

With the goal of understanding corneal biomechanics, techniques to measure the mechanical properties of the cornea have evolved considerably. Two main groups can be differentiated: ex vivo destructive tests, and clinical tests. Within the main clinical tests, two main branches can be differentiated: imaging of the corneal surface and anterior segment (**Corneal Topography**), and measurement of dynamical and mechanical parameters of the corneal tissue (**Non-Contact Tonometry**).

**Corneal Topography**

Different imaging techniques have been developed over the last years.\(^ {24}\) The most common and important is the **corneal topography**,\(^ {25}\) a non-invasive imaging technique for mapping the anterior and posterior surfaces of the cornea (see in Figure 1.4.b-d). Different topographical characteristics of the cornea are evaluated,

- **Height, Sagitta, or Elevation**: pointwise distances from the corneal surface to a reference surface (generally a tangent plane to the corneal apex). Once the corneal shape is retrieved, secondary parameters can be derived (e.g. slope, curvature, or power).
- **Pachymetry**: thickness of the cornea (i.e. difference between anterior and posterior surfaces).
- **Radius of curvature**: characterizes the curvature of the corneal surface (usually expressed in mm).
- **Power**: depends on the curvature of the surfaces, and the refractive index between both sides of the surface (expressed in diopters, D).

\(^ {22}\) Romero-Jiménez et al. 2010, Ambekar et al. 2011

\(^ {23}\) Hassan et al. 2014

\(^ {24}\) Dorairaj et al. 2007, Salomão et al. 2009

Nowadays there are two technologies used to measure corneal topographies: reflection-based systems, and projection-based system. Within this categories, we will focus on two subcategories: Placido-based systems (reflection-based), and Scheimpflug photography-based (projection-based). A more extensive review in clinical devices can be found in Piñero et al. (2014, 2015), or Kaschke et al.

Placido-based systems
Comprises the most widely used category of topographers. The working principle consists in projecting a pattern of concentric rings (Placido's disk) onto the cornea, and measuring the deformation of the reflected pattern. The contour deformation of reflected rings is computationally compared against the reference pattern reflected by a reference surface. The measurement of corneal elevation coordinates \((x, y, z)\) is not directly measured, but the deviation of reflected rings allows for calculating the slope of the corneal surface in axial direction. Hence, elevation maps introduce an indirect error. Furthermore, controlling the smoothness and uniform distribution of the tear film over the corneal epithelium is essential: a tear film break-up could cause inaccurate tracking and artifacts in the corneal maps (e.g. areas of irregularity, or false irregular astigmatism). Furthermore, some limitations of these systems are,

- the lack of real information of the central area (the central ring of the pattern is dark),
- the information is directly given along meridians in radial direction (i.e. no direct information of the corneal geometry is provided in circumferential direction),
- the computational reconstruction algorithms cannot cope with highly irregular corneas, implying errors greater than 4 diopters in very steep or flat corneas, keratoconus with local steepening, sharp transition zones after uncomplicated refractive surgeries, diffusely irregular surfaces after penetrating keratoplasty, and complex surfaces or central islands after decentered laser ablations.

Scheimpflug photography-based systems
The Scheimpflug principle is a geometric rule that gives the orientation of the best plane of focus when the lens plane is not parallel to the image plane (i.e. the opposite to a normal camera system where the plane of focus is parallel to the lens and image planes). Also, it can occur when a planar subject is not parallel to the image plane. In this scenario, an oblique tangent can be drawn from the image, object and lens planes, given the intersection point with best focus of the image (i.e. Scheimpflug intersection). Pentacam system (Oculus, Germany) is one of the most recognized systems based on this principle (see in Figure 1.4.a). Specifically, a rotating Scheimpflug camera captures 50 Scheimpflug images of the
anterior segment in less than 2 seconds. Each image contains 500 true elevation points, giving a total of 25,000 true elevation points for the corneal surface. The main advantages of these systems are,

- the high resolution analysis of the entire cornea (including the center of the cornea),
- the ability to accurately measure corneas with severe irregularities (e.g. keratoconus),
- and the ability to calculate pachymetry maps from limbus to limbus.

Besides, Pentacam system provides more repeatable and reproducible anterior and posterior measurements of corneal power than other technologies. Additional systems based on Scheimpflug photography are Sirius (CSO, Italy) and Galilei (Ziemer Ophthalmic Systems AG, Switzerland). Both combine a 3D rotating Scheimpflug camera with a Placido disk topographer. While the Placido pattern
Introduction provides high accuracy in measuring the curvature, the Scheimpflug camera captures precise elevation data. This combination of technologies allows for a full analysis of the entire cornea and anterior segment. Specifically, Sirius (see in Figure 1.4.c) enables retrieving 25 radial sections of the cornea and anterior chamber in few seconds, measuring 35,632 points of the anterior surface and 30,000 of the posterior surface (in high resolution mode). Furthermore, it provides consistent measurements of curvatures (anterior and posterior), pachymetry, and anterior chamber depth in normal and keratoconus eyes. However, Sirius and Pentacam should not be used interchangeably.

Non-Contact Tonometry

To date, only two commercial systems aim at providing corneal biomechanical data. In 2005, Ocular Response Analyzer (ORA, Reichert Ophthalmic Instrument, see in Figure 1.5.a), a new device for characterizing the corneal biomechanics, was released to the market. Apart from measuring the corneal biomechanics, it was also presented as a device with the capability of obtaining intraocular pressure (IOP) measures less dependent on corneal thickness than applanation tonometers (i.e. Goldmann tonometers). The basis of this instrument is the analysis of the corneal behaviour during a bidirectional applanation process induced by an air jet. As outcomes, two biomechanical parameters are provided: the corneal hysteresis (CH), and the corneal resistance factor (CRF). CH is defined as the difference between the pressure at the first (ingoing) applanation (P1) and the second (outgoing) applanation (P2) recorded during the measurement process (see in Figure 1.5.b). The CRF is calculated using a proprietary algorithm and it is supposed to be related to the corneal elastic properties. Other measures provided are the Goldman intraocular pressure (IOPG, average of P1 and P2), and the corneal-compensated intraocular pressure (IOPCC), theoretically less affected by corneal properties (e.g. the central corneal thickness).

However, as ORA does not provide corneal imaging, an alternative commercial device named after CorVis ST (Oculus, Germany, see in Figure 1.5.c) was developed (2010), on which cross-sectional imaging of the cornea, bidirectional applanation technology, and high-speed photography are combined. Features that have been suggested to be potentially useful for an integral analysis of the cornea, including corneal biomechanics. This device is a non-contact tonometer that uses a high-speed Scheimpflug-camera (4330 frames/sec), along with a biapplanation system, to record the motion of the cornea when subjected to an air jet. Specifically, the cornea passes through distinct phases as it moves: first, the ingoing phase passing from resting shape, through applanation, to a concave shape (i.e. maximum deformation amplitude); second, a short oscillation phase previous to the outgo-

32 Nasser et al. 2012
33 Ortiz et al. 2007, Piñero and Alcón 2014, 2015
34 Hong et al. 2013, Lanza et al. 2016
ing phase, which gives the second applanation, and the final return to the resting state. The main outcomes (corneal biomarkers) are the deformation amplitude of the cornea (i.e. maximum deformation amplitude at the highest concavity), the applanation length and time, the corneal velocity, the IOP, and the corneal pachymetry (see in Figure 1.5.d).

Figure 1.5: Non-Contact Tonometers (ORA and CorVis): (a) ORA; (b) Signal provided by ORA. While the air pressure (solid green line) is applied over the cornea, the infrared signal (solid red line) that detects the applanation triggers 2 times (ingoing and outgoing applanation). The difference of pressure between the ingoing (P1) and outgoing (P2) applanation points gives the corneal hysteresis (CH); (c) CorVis ST; (d) CorVis Graphic User Interface (GUI) showing all the dynamic parameters recorded during the air pressure.

A Bridge between ex vivo Destructive Tests and Simulation

In ex vivo laboratory experiments, corneas are isolated and tested in a stress-driven (or displacement-driven) manner, with a well-controlled constant-humidity environment. The main advantage relies on the possibility of applying different loads, allowing to sweep different tissue behaviours (i.e. uniaxial tension, biaxial tension, shear, or bending). Regarding the cornea, one of the main drawbacks is the disruption of the fibril orientation when corneal slices are tested.\textsuperscript{35} Besides, hydration needs to

\textsuperscript{35} Elsheikh and Anderson 2005, Sancho 2010, Ortillés et al. 2017b
be controlled to match *in vivo* conditions. Although intact corneas can be used in inflation and indentation tests, *in vivo* conditions cannot be fully reproduced.

After obtaining the mechanical properties experimentally, macroscopic mathematical models have been developed to determine the corneal mechanical properties. Some approaches have been used to retrieve the mechanical properties by simulating uniaxial tests, inflation tests, or clinical tests numerically. Coupling both, simulation and clinical experiments, allows to numerically represent the corneal behaviour by means of inverse optimization methods. However, several assumptions must be done due to the individual structural variations, and material properties.

Once a suitable mechanical model of the cornea is achieved, it can be applied to simulate and solve different ophthalmic problems. Pioneers used finite element models to reproduce surgeries, trying to analyze optical changes after radial keratotomy. Despite these models were reasonable accurate, there were some limitations as the inclusion of corneal mechanical changes after the surgery, or microstructural details regarding the collagen fibers network. Recently, other models have approached corneal biomechanical modeling using tonometry values, or considering other anisotropic patterns of the collagen fibers. Not only that, further attempts to simulate refractive surgeries such as PRK laser surgeries, or cataract surgeries have been addressed, also including viscohyperelastic non-isotropic numerical models for fibred tissues.

Despite the great efforts and recent breakthroughs, quantitatively predicting patient-specific outcomes with FE modeling is difficult. To overcome these limitations, second harmonic-generated imaging (SHG) have been used to obtain a detailed microstructural definition of the corneal fibers. The cross-section of the human cornea showed that stromal lamellae did not lie only parallel to the anterior surface, but they present out-of-plane (transverse) anastomosis, connecting different layers, and the central part of the cornea with the limbus. Not only that, but they also present depth-dependent distribution of collagen fibers, depending in the physiological function of the eye. As a consequence, some continuum mechanics models including the out-of-plane lamellae distribution, and the depth-dependence have been developed. Incorporating the spatial variation of the collagen seems to be crucial to accurately model some specific deformation modes. Nevertheless, they cannot completely represent the complex collagen architecture found in the human corneal stroma.

Finally, and in the vein of including the most ground-breaking techniques, two powerful and flexible numerical tools have been lately incorporated to computational ophthalmology: fluid-structure interaction (FSI) simulations, and tissue remodeling algorithms. The aim of FSI simulations is to couple the mechanical simulation of the solid, with the fluid simulation of the environment surrounding it. In this vein,
some ophthalmic simulations have been carried out involving impact effects, or the effect of the intraocular pressure. Currently, and to the best of the author’s knowledge, only dynamic effects have been accounted for when simulating non-contact tonometry, and no FSI simulations have been carried out yet. Concerning tissue remodeling algorithms, they have been widely applied to different biological problems. However, regarding Ophthalmology, only a few applications have been addressed and mainly related with scleral tissue growth. Then, applying these techniques to corneal biomechanics is still a promising field to explore. Still nowadays, the mechanical characterization of the cornea has not been properly solved, either macroscopically or microscopically.

1.4 Project Framework

The present thesis has been developed within the framework of two research projects,

POPCORN Project: Development of corneal biomechanical model. Dynamic topographical characterization based on 3D plenoptic imaging. (FP7-SME-2013 Research for SMEs, Grant Agreement number 606634)

POPCORN’s main objective was to develop a non-invasive corneal system to characterize the corneal biomechanics, and to predict the mechanical changes of the corneal structures after different detrimental actions (e.g. surgical interventions). A new technological process aimed at generating the personalized biomechanical model of the patient’s cornea in vivo, to predict the corneal behavior after surgery. The final goal was to detect and avoid possible risks, and negative side effects, that could lead to additional treatments or long-term consequences for the patient’s visual health.

Non-Invasive plenoptic imaging techniques were planned to be used to generate the in vivo patient-specific model of the cornea. Furthermore, until now, assessing the biomechanical properties of the corneal tissue in the clinical practice was limited to the measurement of the parameter called Corneal Hysteresis (provided by the Ocular Response Analyzer, ORA). Clinicians that cannot afford to access to this commercial system are limited to measure geometric aspects of the cornea so as to infer some assumptions about the biomechanical status of the cornea. In this vein, POPCORN also aimed at including computational tools to assess on the mechanical properties of the cornea based on the corneal motion.

In brief, the project focused on the following research and development steps,

- Development of the dynamical corneal topographer prototype by integrating a
plenoptic system for 3D imaging the cornea that enables to warp the cornea.

- Development of the algorithms for transforming depth information of the corneal surface in topographic parameters for corneal topography.
- To determine biomechanical parameters of the in vivo cornea before, during, and after deformation.
- Using a computational system in the cloud, to determine the corneal behaviour after a surgical intervention based on a non-linear anisotropic hyperelastic finite element model.
- Clinical validation of the biomechanical models.

The POPCORN project included 7 partners from 3 different European countries, including small and medium enterprises (SMEs) and Research Technological Developers (RTD). The consortium was coordinated by OFTALMAR (Alicante, Spain). Four SMEs aimed at forming a supply chain for production of the POPCORN system,

- Optoelectronica 2001 (Manufacturing), Romania (http://www.optoel.ro)
- Biotronics 3D (Software), United Kingdom (http://www.biotronics3d.com)
- CSO (Marketing and distribution), Italy (http://www.csoitalia.it)
- OFTALMAR (Clinical validation and advise), Spain (http://www.oftalmar.es)

Three RTDs aimed at covering the skilled gap in mathematical models, optics, and software development,

- ISRI (UK Intelligent Systems Research Institute) (Electro-mechanical system), United Kingdom (http://www.uk-isri.org/)
- AIDO (Optical system), Spain.
- I3A-University of Zaragoza (Mechanical models), Spain (http://i3a.unizar.es/es)

The duration of the project was 30 months, and it finished in March 2016.

**Role of the AMB Research Group (University of Zaragoza)**

Our research group, Applied Mechanics and Bioengineering, took part in two different work packages (WP4 and WP5), whose objectives were,

- To create in silico finite element models and meshes of the cornea.
- To develop the methodology to simulate and analyze physiological mechanisms of the eye.
• To generate patient-specific finite element models based on data provided by topographers.

• To evaluate the biomechanical parameters of healthy corneal tissues applying finite element inverse analysis.

• To generate a predictive model of the mechanical response of the cornea after different refractive surgeries.

**Corneal tissue response to cross-linking treatment. Application to keratoconus treatment (DPI2014 - 54981R)**

This project is focused in the *in vivo* characterization of corneal tissue. The main aim is to establish new biomarkers to diagnose pathologies associated to its weakening: keratoconus or keratitis produced by Acanthamoeba. The global objective of the project is to design a new methodology that allow for evaluating the mechanical behavior of the corneal tissue *in vivo*, so as to assess in the early diagnosis of pathologies linked to the tissue weakening, as well as the evaluation of the Cross-Linking treatment.

Among all the tasks, those directly related with the present thesis are,

• To develop a methodology to determine the hyperelastic behavior of the corneal tissue (*in vivo* and in an animal model) by means of combining experimental tests and inverse analysis for the identification of the mechanical parameters.

• To advance in the understanding of the structural changes produced in the corneal tissue during the evolution of keratoconus, and its relation with the mechanical behavior. To develop a numerical model that allows for qualitatively predicting the temporal evolution of the disease, and the effect of the feasible treatments.

**Personal Funding**

*Contrato Predoctoral del Gobierno de Aragón (DGA)*

M. Á. Ariza-Gracia received funding (4 years, of which only 2 were used) from the Governor of Aragón (Diputación General de Aragón, DGA) to carry out the research project entitled "*Modelos Computationales Paciente Específico de la Córnea: Aproximación a Modelos Predictivos de Comportamiento para la Valoración Ocular Fisiológica y Ectásica*" (Patient-Specific Computational Models of the Cornea: Approximation to Predictive Models of Behavior to the Physiologic and Ectatic Ocular Assessment).
Ibercaja-CAI mobility program

M. Á. Ariza-Gracia received funding (3 months) from the Ibercaja-CAI mobility program to perform a research stay at Politecnico di Milano (Milano, Italy) to carry out the research project entitled "Modelos Computationales Paciente Especifico de la Córnea: Ayuda al Diganóstico y Planificación de Tratamientos" (Patient-Specific Computational Models of the Cornea: Help to Diagnosis and Treatment Planning).

ESKAS Scholarship (Excellence Scholarships for Foreign Students, Swiss Government)

M.A. Ariza-Gracia was awarded with the swiss ESKAS scholarship (rate of success < 15%) to perform a research stay (1 year) at University of Bern (Bern, Switzerland) to develop the research project entitled "On a Novel Approach to Accurately Determine the Human Patient-Specific Corneal Tissue Behaviour Based On Experimental, Computational and Machine Learning Techniques" (ESKAS-Nr: 2016.0194).

1.5 Motivation

The corneal shape is the result of the equilibrium between its mechanical stiffness (related to the corneal geometry and the intrinsic stiffness of the corneal tissue), intraocular pressure (IOP), and the external forces acting upon it such as an external pressure (see in Figure 1.6).

An imbalance between these parameters, for example,

- an increment of IOP,
- a decrement of the corneal thickness induced by refractive surgery,
or by a corneal material weakening due to a disruption of collagen fibers, can produce ocular pathologies (ectasias) which seriously affect patient’s sight. Consequently, it is important to understand how these ocular factors are related to pathologies in order to improve treatments. In order to do that, different corneal features must be properly characterized,

- Physiological conditions of the eye: intraocular pressure (IOP), and interaction of the eyeball with the surrounding media,
- Patient-specific corneal geometry,
- Patient-specific mechanical properties of the eye.

To date, IOP can be measured using contact tonometers (e.g. Goldmann Applanation Tonometry), whereas corneal topography is obtained with corneal topographers (e.g. Pentacam, or Sirius). The availability of high resolution topographical data and patient’s IOP have made possible to reconstruct patient’s specific geometric models. In this regard, some patient-specific models have already been reported in the literature. However, the workflow described in these studies cannot be automated in a straightforward manner as to permit personalized analysis on large populations.

Non-contact tonometry (e.g. CorVis ST, Oculus Optikgeräte GmbH) has recently gained interest as a diagnostic tool in ophthalmology as alternative method for characterizing the mechanical behavior of the cornea. In a non-contact tonometry test, a high-velocity air jet is applied to the cornea for a very short time (less than 30 ms), causing the cornea to deform, while the corneal motion is recorded by a high-speed camera. A number of biomarkers associated with the motion of the cornea, i.e., maximum corneal displacement and time between first and second applanations, among others, have been proposed to characterize pre- and post-operative biomechanical changes.

As the dynamic response is the result of the interplay between different corneal features (IOP, geometry, material), it is reasonable to argue that a misunderstanding of the diagnostic tools is likely to be the cause of the unexpected clinical results already occurring (e.g. a softer cornea with a higher IOP could show the same behavior as a stiffer cornea with a lower IOP). Although geometry and IOP can be already measured accurately, the mechanical behavior of the cornea cannot be directly characterized in vivo.

Precise knowledge about the underlying factors that affect the corneal mechanical response will allow establishing better clinical diagnoses, monitoring the progression of different diseases (e.g., keratoconus) or designing a priori patient-specific surgical plans that may reduce the occurrence of unexpected outcomes.
The aim of this thesis is to stride towards methodologies to determine the patient-specific geometry and mechanical properties of the cornea. Shedding light on Patient-Specific Corneal Biomechanics will allow to perform personalized assessment in ocular surgeries and treatments, trying to ease the current unexpected optical outcomes.

1.6 Objectives

The global aim of the thesis can be split into different objectives depending on each project framework. Regarding the objectives of the POPCORN Project,

- **To understand the Corneal Biomechanics paradigm.** How is cornea working? How do the different parameters interplay between them? The first objective is to review the up-to-date state of the art, and to perform an *in silico* average model to show how different corneal factors (IOP, material, and geometry) would affect in the motion of the corneal apex during a general non-contact tonometry.

- **To reconstruct Patient-Specific Corneal geometries.** Does the use of Patient-Specific Corneal Geometries really matter? The second objective is to develop a numerical algorithm capable of processing corneal topographies automatically. Using the data provided by corneal topographers, the numerical pipeline must be able to reconstruct a finite element (FE) model. The FE model must incorporate the different external structures of the eye (patient-specific cornea, limbus, and sclera), and the anisotropic mechanical behavior of the cornea. Finally the model must be used to reproduced an *in silico* non-contact tonometry test.

- **To determine the Patient-Specific mechanical properties of the cornea.** Can Patient-Specific Tissue Properties be retrieved from clinical tests? The third objective is to determine the patient-specific mechanical properties of the cornea using clinical experimental tests (i.e. non-contact tonometry), *in silico* simulations, and optimization methodologies.

- **To generate a predictive model of the mechanical response of the cornea.** Can Corneal Behavior be predicted based on our previous knowledge? The fourth and final objective is to use the proposed *in silico* workflow to predict the mechanical properties of the cornea in clinic. In order to do that, the numerical methodology was automatically applied to build a dataset of \( \approx 10,000 \) cases. Subsequently, different mathematical strategies were applied to infer the mechanical properties of the cornea based only on clinical biomarkers: Goldmann applanation tests, Corneal topography, and Non-Contact Tonometry.

Additional objectives are derived from the Spanish project "Corneal tissue response to cross-linking treatment. Application to keratoconus treatment".
• To establish an alternative methodology to characterize corneal tissue. Is one experiment really enough? Kok et al.56 outlined that using a single test to characterize corneal tissue was an ill-posed problem. The fifth objective is to establish an alternative numerical-experimental protocol that allows for a better characterization of the corneal tissue. Two sets of experiments were proposed to characterize the tension and bending mechanical behavior of the cornea. A refractive surgery (Astigmatic Keratotomy) was used to validate the methodology.

• To extend computational simulations to cope with fluid-structure interaction simulations. Is a structural simulation accurate enough? Does the inclusion of the surrounding fluids affect the simulations? The sixth objective is to determine whether including the effect of the air jet as a pure load on the model, or including the effect as the air jet as a fluid interacting with the cornea modifies the results of simulations. Additionally, different boundary conditions are analyzed to calibrate their impact on the outcomes of the simulations.

1.7 Organization of the Thesis

The thesis follows a traditional chapter-wise organization. Chapters 2 to 6 correspond to already published (or under peer-reviewed process) scientific papers and, therefore, follow a self-contained journal scheme (Introduction, Material and Methods, Results, and Discussion). Chapter 7 contains the contributions of the research to the field, and the future lines. Appendices gather all the additional information needed to understand the complete scope of the work.

Ch. 1 Introduction. Scope, motivation, and objectives of the present thesis.

Ch. 2 Foundations of Corneal Biomechanics. This chapter copes with the basic knowledge of what ‘Corneal Biomechanics’ is, and how it is related to non-contact tonometers. Besides, an average in silico model is built to outline the impact of the most important corneal physical features (intraocular pressure, geometry, and material) on the corneal displacement during an air jet load. All the related information of this chapter is published in ‘Coupled Biomechanical Response of the Cornea Assessed by Non-Contact Tonometry’ (PLoS One, 2015. Impact Factor (IF): 3.057. Q1, Web of Knowledge (InCite JCR).).57

Ch. 3 Patient-specific Geometry. This chapter copes with the development of a numerical algorithm capable of reconstructing patient-specific geometries, and simulating non-contact tonometry tests automatically. All the related information of this chapter is published in ‘Automated Patient-Specific Methodology for Numerical Determination of Biomechanical Corneal Response’ (Annals of Biomedical Engineering, 2016. IF: 3.221. Q1, Web of Knowledge (InCite JCR).).58
**Ch. 4 Patient-specific Material Prediction.** This chapter copes with the generation of a prediction model for the mechanical properties of the corneal tissue. All the related information of this chapter is published in ‘A Predictive Tool for Determining Patient-Specific Mechanical Properties of Human Corneal Tissue’ (Computational Methods in Applied Mechanics and Engineering, 2016. *IF*: 3.949. *Q1*, *Web of Knowledge* (*InCite JCR*).).

**Ch. 5 Numerical-Experimental Protocol to Determine Corneal Properties.** This chapter copes with the development of an alternative numerical-experimental protocol to determine the mechanical properties of the corneal tissue. Besides, the prediction of refractive surgery is carried out to validate the methodology. All the related information of this chapter is published in ‘A Numerical–Experimental Protocol to Characterise the Corneal Tissue with Application to the Prediction of an Astigmatic Keratotomy Surgery’ (Journal of the Mechanical Behaviour of the Biomedical Materials, 2017. *IF*: 3.110. *Q2* (percentile 74.675), *Web of Knowledge* (*InCite JCR*).).

**Ch. 6 Fluid-Structure Interaction Simulation of a Non-Contact Tonometry.** This chapter addresses the study of the necessity of fluid-structure interaction simulations, and the impact on the simulation of non-contact tonometry tests. All the related information of this chapter is under preparation (submission to the Journal of Biomechanics and Modeling in Mechanobiology, 2017. *IF*: 3.323. *Q1*, *Web of Knowledge* (*InCite JCR*).).

**Ch. 7 Outcomes and Future Lines.** This chapter contains the main conclusions of the current work, and research lines that are currently opened and constitute the main future lines of a post-doctoral research.

**App. A Sumario y Conclusiones en Español.** This appendix contains the translation of the Summary and Conclusions to Spanish (required by University of Zaragoza).

**App. B Publications.** This appendix contains the title page of those articles already published.

**App. C Material Models.** This appendix contains all the information concerning the constitutive models needed to reproduce the results showed in the present thesis.

**App. D Artificial Ray-Tracing in Optical Systems (ARiOS).** In this thesis, methodologies to reproduce patient-specific geometries and simulation of surgeries are addressed. To validate, a software to perform optical validations (ARiOS) has been developed. This appendix contains all the information regarding the mathematical assets required, how to use it (input files), and its validation against commercial software (OSLO).
2

Foundations of Corneal Biomechanics

Because of this, originality consists in returning to the origin.

Antonio Gaudí

This chapter contains with the basic knowledge of what “Corneal Biomechanics” is, and how it is related to non-contact tonometers. Besides, an average in silico model is built to outline the impact of the most important corneal physical features (intraocular pressure, geometry, and material) on the corneal displacement during an air jet load.

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2.1 Introduction

The shape of the cornea is the consequence of the equilibrium between its mechanical structure and the forces acting upon it. The mechanical behavior of the cornea depends on its geometry (thickness, curvature and topography) and material properties, which in-turn relies on the microstructure of the stroma. The combination of high-speed photography (Scheimpflug imaging) of corneal images and dynamic bidirectional applanation technologies has been recently proposed as a new potentially useful method for evaluating the mechanical behavior of the cornea. These devices, known as non-contact tonometers, record the corneal motion while an air pulse forces the deformation, and report the deformation amplitude of the cornea, the applanation length and the corneal velocity over time. Likewise, intraocular pressure (IOP) and corneal apical pachymetry data, e.g. corneal central thickness (CCT), are also provided.

To date, a limited number of studies evaluating the clinical application of non-contact tonometers have been performed. Huseynova et al. found a low but moderate correlation of IOP with deformation amplitude of the cornea (Pearson’s correlation coefficient $\rho = -0.360$, $p < 1e^{-4}$), applanation time ($\rho = -0.540$, $p < 1e^{-4}$) and applanation velocity ($\rho = -0.118$, $p < 1e^{-4}$). Unfortunately, they did not report any correlation of corneal central thickness (CCT) with the deformation amplitude of the cornea. In a recent review, Roberts states that IOP is the strongest predictor of corneal deformation amplitude, followed by corneal stiffness, and CCT being the less influential along with the curvature. Valbon et al. reported a weak correlation between the highest concavity-time (the time at which the highest concavity of the cornea is reached) and age for healthy eyes. In addition to the work performed on healthy eyes, Faria-Correia and co-authors have found that ocular hypertension in pressure-induced stromal keratopathy is associated with lower deformation response. However, there is no scientific evidence showing the relationship between the analysis of the response to the air-puff and the parameters characterizing the mechanical properties of corneal tissue.

Patient specific geometrical models are useful for performing a diagnosis test. This gives doctors the opportunity of improving their diagnosis by relying on real patient data, rather than in a generalized statistical atlas. Late eyeball models already use patient-specific models based in Zernike interpolation and point cloud data reconstruction obtained from a topographer in order to represent a specific cornea for each patient. In this work, an automatic methodology that generates a patient-specific corneal model is used.

Besides, the in vivo human cornea is a porous tissue with high water content (approximately 80% of the corneal weight is due to water). Among the five layers that constitute the cornea, the stroma forms about 90% of the thickness and is com-
posed of long collagen fibers embedded in a ground substance mainly formed of proteoglycans and water. Collagen fibers lie parallel to the corneal surface and are orthogonally disposed along the superior-inferior and nasal-temporal directions whereas they are predominantly circumferential near the limbus. This microstructure and the different distributions of collagen fibers give the corneal tissue an anisotropic mechanical behavior. Therefore, the constitutive material behavior of the cornea was considered as anisotropic hyperelastic accounting for the two families of collagen fibers present in the eye.\textsuperscript{12}

A finite element (FE) analysis of a non-contact tonometer is performed. This simulation was not intended to reflect any commercial device, but only to replicate a typical evaluation test. In this regard, the characteristic of the test, i.e., peak pressure of the air-puff, and the location and duration of the air pulse, were set in order to emulate a general non-contact tonometer, since the aim of the study is to better understand the relation that the corneal material behavior, IOP, and pachymetry have with the deformation that the cornea experiences when subjected to this type of diagnosis test.\textsuperscript{13}

In order to achieve this objective, different sets of experiments were designed. The influence of the IOP has been studied by considering four pressure levels (10 mmHg, 12 mmHg, 19 mmHg and 28 mmHg) and three different levels of corneal stiffness (low (material A), intermediate (material B) and large (material C) stiffness) taking into account the material ranges reported in the literature. In addition, the relation between the CCT and the maximum apical displacement during an air puff diagnostic test was studied by varying the CCT from 300 microns to 600 microns along with the corneal tissue stiffness variation (material A, material B and material C) and three levels of IOP (10 mmHg, 19 mmHg, 28 mmHg). As final goal, this study seeks to gain a better understanding of the coupling existing between the aforementioned parameters in order to better interpret the results obtained with a non-contact tonometry test.

\section{2.2 Material And Methods}

\textit{Corneal Geometry and Patient-Specific Corneal Finite Element Model}

The right healthy cornea of a 25-year man was considered in the study (data shown in Table 2.1). The individual in this manuscript has given written informed consent (as outlined in PLOS consent form) to publish these case details. All procedures were carried out under project license of POPCORN project approved (31st October, 2013) by the Ethics Committee of the Research of the University of Alicante (Comité de Ética de la Investigación de la Universidad de Alicante, CEUA). The corneal topographic map reconstructed using a Pentacam system (Oculus Op-
tikgeräte GmbH, Germany) showed the conventional bow-tie pattern, without significant asymmetry. The main parameters were: a central corneal thickness (CCT) of 585 microns and a Goldmann IOP of 12 mmHg.

<table>
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<th>IOP</th>
<th>12 mmHg</th>
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<td>Apex Pachymetry</td>
<td>585 microns</td>
</tr>
<tr>
<td>Min. Pachymetry</td>
<td>583 microns</td>
</tr>
<tr>
<td>Corneal Volume</td>
<td>63.5 mm³</td>
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<table>
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<th>Corneal Astigmatism</th>
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<th>Posterior Surface</th>
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<td></td>
<td>0.4 D</td>
<td>0.3 D</td>
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<tr>
<td>Corneal Asphericity</td>
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<td>-0.12</td>
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<tr>
<td>Average Radius</td>
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<td>6.64 mm</td>
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A three-dimensional finite element model of the anterior half ocular globe geometry, which accounts for three different parts: the cornea, the limbus and the sclera, was considered (Figure 2.1.a). A methodology for constructing patient specific corneal models has been used which allows building the patient specific model of the cornea by using the topography of the anterior surface of the cornea and the pachymetry data.

![Finite element model of the eye](image)

Real data was kept at those points where topographical data was available (see the pachymetry map in Figure 2.2.a), whereas a quadric surface was used to complete the cornea up to a mean diameter of 12 mm (see the grey area in Figure 2.2.a). In order to further demonstrate the patient-specific characteristics of the model, the difference between the patient’s and numerical pachymetry used in the FE model is shown in Figure 2.2.b. As it can be observed, the patient-specific is fully achieved in those points where data were known (see blue area belonging to 0% error difference), obtaining only a maximum error difference of a 7.5% at the joint between the quadric surface (see green area in Figure 2.2.b) and the real surface. This error is related to the smoothing algorithm used to joint both surfaces in order to avoid numerical problems due to surface discontinuity. In addition, a 25 mm, in average,
diameter sphere was considered for the sclera, whereas the limbus is a ring linking both, sclera and cornea. Axial displacements and rotations were restrained at the bottom surface of the sclera.\textsuperscript{17}

A mesh composed of 13,425 quadratic full integration mixed formulation solid elements and 62,276 nodes was used to perform the simulations. To test the quality of the mesh used for the calculations, a sensitivity analysis was performed. Table 2.2 shows the change in the apical displacement ($\Delta U$) and maximum principal stress ($\Delta PS$) in the cornea for different mesh densities. The results show that for a mesh size above approximately 60000 nodes, the changes in the apical displacement are less than a 0.05\%, whereas for the maximum principal stress is less than 2.0\%, demonstrating the adequacy of the used mesh.

<table>
<thead>
<tr>
<th>Number of Nodes</th>
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<th>Relative Change in maximum principal stress (%)</th>
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<tr>
<td>27,800</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
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<td>62,276</td>
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</tr>
<tr>
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<td>1.5</td>
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\textbf{Constitutive model for eyeball’s tissue}

The cornea was considered as an anisotropic hyperelastic material with two preferred material directions\textsuperscript{18} (see in Figure 2.1.b) modeled using a Gasser-Holzapfel-Ogden’s\textsuperscript{19} (G-H-O) constitutive equation (2.1).
$\psi_C = \frac{1}{D} \cdot \left(\frac{I_{el}^2 - 1}{2} - \ln(J_{el})\right) + C_{10} \cdot (I_1 - 3) + \frac{k_1}{2 \cdot k_2} \cdot \sum_{\alpha=1}^{N} \{\exp[k_2(\bar{\varepsilon}_a)^2] - 1\}
\bar{\varepsilon}_a \overset{\text{def}}{=} \kappa \cdot (I_1 - 3) + (1 - 3\kappa) \cdot (I_{4(aa)} - 1),
\tag{2.1}
$

where $I_1$ is the first invariant of the modified right Cauchy-Green tensor $\bar{\mathbf{C}} = J_{el}^{-2/3} \mathbf{C}$, $J_{el}$ is the elastic volume ratio, $I_{4(aa)}$ is a pseudo-invariant that represents the square of the stretch along the direction of the $\alpha$th family of collagen fibres, being $N$ the total number of families of collagen fibres (two for the human cornea). $D$ represents the inverse of the volumetric modulus. The dispersion parameter, $\kappa$, ($0 \leq \kappa \leq \frac{1}{3}$) determines the anisotropic grade: $\kappa = 0$ implies transversely isotropy, and $\kappa = 1/3$ implies isotropy. In addition, Eq. 2.1 assumes that collagen fibres only work under traction, i.e. $\bar{\varepsilon}_a > 0$.

Three sets of material parameters associated with: low (material A), intermediate (material B) and large (material C) stiffness, were considered in our simulations (Table 2.3). These sets of parameters span the experimental IOP (mmHg) – Apical Rise (mm) curves response obtained from inflation tests on human corneas20 (see in Figure 2.3).

Figure 2.3: Human corneal response of the constitutive model. (a) IOP (mmHg) vs. Apical Rise (mm). Human range (grey shadow) obtained from inflation test in human corneas [Elsheikh et al., 2008a,b]. Colored lines correspond to inflation response for the three material selected for the numerical simulation: low(material A) – red, intermediate(material B) – blue, large(material C) – green); (b) Uniaxial stress-stretch behavior for the three studied materials.

The viscoelastic behavior of the tissue was neglected since a very fast applied load, as the case of the air-puff, will result in an almost pure elastic response during the loading,21 and corneal hysteresis is observed only during the unloading phase of the air-puff load only affecting the recovery response of the cornea (which is not the objective of this study). Limbus’ material parameters have been assumed identical.

20 Elsheikh et al. 2008a,b. Whitford et al. 2015
21 Simo 1987
Methods for Characterising Patient–Specific Corneal Biomechanics

Cornea and Limbus

<table>
<thead>
<tr>
<th>Mat.</th>
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<th>$C_{10}$</th>
<th>$D$</th>
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<th>$k_2$</th>
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<table>
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Table Legend and Units. $C_{10}$ (MPa): material parameter related to the extracellular matrix; $D$ (MPa$^{-1}$): volumetric term; $k_1$ (MPa) and $k_2$ (–): material parameters related to the collagen fibers; $\kappa$ (–): degree of dispersion of the fibers; $Y_{i0}$ (MPa): material parameters related to the sclera.

Table 2.3: Material parameters for cornea, limbus, and sclera.

Sclera

as for the cornea. The sclera was considered as an isotropic hyperelastic material (Table 2.3) and was modeled using the Yeoh’s constitutive model (2.2).22

$$\psi_Y = \sum_{i=1}^{3} \frac{1}{D_i} (J_{el} - 1)^{2i} + \sum_{i=1}^{3} Y_{i0} \cdot (I_1 - 3)^i,$$  

(2.2)

Non-contact tonometer simulation

Since the patient’s eye is subjected to the IOP when the topographical data is acquired, the prior step to simulating the non-contact tonometry test is the identification of the initial stress-free configuration of the eye. An iterative zero pressure algorithm was applied in order to obtain the initial free-stress configuration of the eye in each simulation.23 The algorithm applies an IOP to an initial free-stress geometry ($X_{init}^k$) for obtaining the first deformed configuration ($x_{def}^k$). Once the pressurization ends, the difference error between the deformed configuration and the topographer’s geometry ($X_{ref}^0$) is computed ($E^k = x_{def}^k - X_{ref}^0$). If the infinite norm of the error ($e^k = \|E^k\|_\infty = \max(E^k)$) is higher than a given tolerance ($\epsilon$), a new initial configuration is computed ($X_{init}^{k+1} = X_{init}^k - E^k$). Otherwise, the initial configuration obtained is such that when it is pressurized to IOP, it achieves the measured configuration. For the simulation of the non-contact tonometry test, the air-puff was assumed as a metered collimated air pulse with a peak pressure of 25 kPa ($\approx$ 180 mmHg) and 30 ms duration, with a profile given in Figure 2.4.a (personal communication with Oculus).

The air-puff spatial pressure (see Figure 2.4.b) was obtained from a CFD simulation performed with the commercial software ANSYS (see Figure 2.5a–b) in order to load the corneal as close to reality as possible. As shown in 2.5a–b, the desired peak pressure applied to the cornea lies on an approximated circular area of 3 mm
in diameter.

A total of 41 numerical experiments were performed to study the influence of: i) IOP, ii) corneal thickness, and iii) material behavior (stiffness), on the maximum corneal displacement. Numerical simulations have been performed on the finite element software ABAQUS (Dassault Systemes), using a conventional personal computer (8-cores i7-4770 3.4 GHz, 8 GB RAM) requiring a computation time of approximately 45 minutes to perform a full simulation. Visualizations of the results carried out with the software ParaView (Kitware Inc. and Los Alamos National Laboratory).\textsuperscript{24}

2.3 Results

Figure 2.6 shows the deformation amplitude of the corneal apex for different IOP and different corneal material response. The corneal deformation following the air pulse varies linearly with IOP, with larger displacements corresponding to lower IOP.
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Figure 2.6: Displacement – Pressure response of the corneal apex. Vertical displacement of the corneal apex (mm) as a function of IOP (10, 12, 19 and 28 mmHg) for the three material models: low (material A), intermediate (material B), large (material C) stiffness.

Figure 2.7 shows that different combinations of material parameters (within the reported human range\(^{25}\)) and IOP could produce the same apical displacement (see the overlapping area in Figure 2.7).

This fact is better demonstrated in Figure 2.8 showing the temporal evolution of the displacement of the apex for three values of IOP (10 mmHg, 19 mmHg and 28 mmHg) and the three analyzed corneal mechanical properties (only half of the time history is shown). This figure also shows the maximum apical corneal displacement corresponding to the patient’s IOP=12 mmHg, depicted as inverted triangles, for all three materials. An overlapping zone can be observed for two of the chosen materials: the softest material coupled with the highest IOP, and the intermediate stiffness material with the lowest IOP. On the contrary, there is a gap zone between the most rigid material and the intermediate stiffness material (see overlapping zone and gap in Figures 2.7 and 2.8). Hence, different combinations of IOP and material stiffness may lead to the same maximum displacement of the corneal apex indicating the existence of a coupling between the effect of corneal material behavior and the IOP.

Figure 2.9 shows the effect of corneal thickness on the maximum apical displacement. In general, as the thickness decreases below 500 microns, the maximal corneal displacement increases rapidly, reaching values up to three times larger for corneal thickness below 400 microns. A closer analysis of the results show a cubic relationship (right panel on Figure 2.9) between the maximum apex displacement and the corneal. This cubic relationship was found independently of either the material stiffness or the IOP. For a given material stiffness, the influence of corneal thickness on the maximum apical displacement is cubic.

\(^{25}\) Elsheikh et al. 2008a,b
Figure 2.7: Displacement – Pressure: response overlapping. Overlapping zone in the corneal response (grey zone) where different combinations of IOP and material lead to the same displacement.

![Figure 2.7: Displacement – Pressure: response overlapping. Overlapping zone in the corneal response (grey zone) where different combinations of IOP and material lead to the same displacement.](image1)

Figure 2.8: Time course of the apex displacement for the conducted simulations. All simulations were performed at three different levels of IOP (10, 19 and 28 mmHg), and three levels of material stiffness: low stiffness (material A, Displacement’s region 10-28 mmHg, red colored area), medium stiffness (material B, Displacement’s region 10-28 mmHg, blue colored area), and large stiffness (material C, Displacement’s region 10-28 mmHg, green colored area). Different overlapping zones, at different loading time, can be observed in figure. Inverted triangles correspond to simulations performed with the real IOP (12 mmHg) and the three different corneal material models.

![Figure 2.8: Time course of the apex displacement for the conducted simulations. All simulations were performed at three different levels of IOP (10, 19 and 28 mmHg), and three levels of material stiffness: low stiffness (material A, Displacement’s region 10-28 mmHg, red colored area), medium stiffness (material B, Displacement’s region 10-28 mmHg, blue colored area), and large stiffness (material C, Displacement’s region 10-28 mmHg, green colored area). Different overlapping zones, at different loading time, can be observed in figure. Inverted triangles correspond to simulations performed with the real IOP (12 mmHg) and the three different corneal material models.](image2)
thinning is more prominent as the IOP decreases (green lines in Figure 2.9). On the contrary, this effect seems to be less acute when the corneal stiffness decreases while IOP remains constant (solid lines in Figure 2.9). This figure also shows the interplay between the corneal geometry, the corneal mechanical properties, and the IOP by which different combinations of these variables could lead to the same maximum apical displacement.

Figure 2.9: Displacement of the corneal apex (mm) as a function of the corneal thickness (CCT). Patient’s pachymetry was constantly decreased for the simulations. Results show a cubic relation between displacement and CCT when the material was fixed (large stiffness material – C). Three levels of IOP were considered: 10 mmHg (dotted-dashed green line), 19 mmHg (solid green line), and 28 mmHg (doted green line). Results also show a cubic relation between displacement and CCT when the IOP was kept at 19 mmHg and the three corneal stiffnesses were considered: low (material A) solid red line, intermediate (material B) solid blue line, and large (material C) solid green line. The right panel shows the accuracy of the fit (minimum mean squares) and the constants of the cubic polynomial.

Figure 2.10 shows the deformed shape of the cornea’s central section at the instant of first applanation and of highest concavity (Figure 2.10.a and Figure 2.10.b, respectively). In addition, the logarithmic hoop strain and the hoop Cauchy stress at highest concavity time are depicted in Figure 2.10.c-d (plotted on the non-deformed configuration for a more clear representation). The figure shows that during the air-puff the cornea experiences bending and, therefore, the anterior surface works in compression (see blue zone in Figure 2.10.c-d) whereas the posterior surface works under tension (see red zone in Figure 2.10.c-d). This means that the collagen fibers in the anterior surface do not contribute to load bearing after the first applanation, since they only work under traction (as in the case of a rope). Hence, at those points the material response depends only on the compressive behavior of the stroma.

Results from Figure 2.10 are demonstrated further in Figure 2.11, where the stress-stretch path followed by a point located at the apex (inverted triangle) and its mirror image on the posterior surface (square) during air-puff are depicted. At the beginning of the test (empty circle on the stress-stretch curve) both points are subjected to traction ($\sigma > 0$, $\lambda > 1$) due to the effect of the IOP. However, during the air-pulse, the state of stress in the anterior surface changes from a traction state to a com-
pression state (see the trajectory of the inverted triangle in Figure 2.11), whereas
the posterior surface remains in traction (open red square).

### 2.4 Discussion

Modern clinical methods for evaluating the biomechanics of the cornea are based
on studying the deformation of the cornea when subjected to the action of a me-
tered collimated air pulse with symmetrical configuration applied at the apex of the
cornea.\(^26\) This \textit{in silico} study conducted on a patient-specific patient eye geometry
seeks to gain a better understanding of the interplay between the structural
characteristics of the cornea, its material behavior, and loading on the mechanical
response of the cornea when subjected to an air-puff. For corneal stiffness within
the observed physiological range, the maximal corneal displacement was found
to follow a linear relation with IOP. In addition, the range of the maximum apical
displacement from the numerical simulation was in good agreement with the maxi-
mum apical displacement reported in a study with 89 healthy eyes, i.e., 0.78 – 1.26
mm, using the CorVis ST system. In the study by Valbon et al.\(^27\) the IOP and
CCT ranged between 7 and 32 mmHg and between 463 and 605 microns respec-
tively. Huseynova et al.\(^28\) studied the influence of IOP and CCT on the different
markers provided by the CorVis ST system. These authors found that the defor-
mation amplitude of the cornea varied between 0.9 and 1.3 mm in the subgroup
of the analyzed sample (III group) having a corneal-compensated intraocular pres-
sure (IOPcc) between 18 and 21 mmHg and a CCT between 555 and 600 microns.
These experimental results on healthy eyes are also within the results reported in

\(^{26}\) Hon and Lam 2013, Dorronsoro et al. 2012

\(^{27}\) Valbon et al. 2013

\(^{28}\) Huseynova et al. 2014
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Figure 2.11: Stress strain response of anterior and posterior apical points during non-contact tonometry. Normal Cauchy Stress vs. stretch path along the meridional direction followed by two points on the anterior and posterior surface of the cornea during air-puff for an IOP = 19 mmHg and the stiffest material (c). Blue color is associated with compression whereas red color is associated with tension. At the physiological configuration when the eye is subjected to IOP (open circle at the beginning of the air jet profile, shown in the inset) the cornea only experiences traction (membrane tensional state). As the air-pulse progresses (black filled circle in the pressure profile inset), the anterior corneal surface (inverted open triangle) experiences compression ($\lambda < 1$) whereas, the posterior corneal surface (open square) experiences a larger tensional stress ($\lambda > 1$).

Our study, confirming the soundness of our model for simulating the corneal response under the action of an air-puff. According to our simulations, the maximum displacement of the apex due to the air pulse varies linearly with IOP for all corneal stiffness considered, with the largest displacement corresponding to the lowest IOP value. This result was consistent with previous results, where a moderate negative correlation between IOPcc and maximum corneal deformation was also found ($r = -0.362, p < 1e^{-4}$). A similar conclusion was stated in the experimental study conducted by Kling et al. Hence, the results of the simulations suggest that the mechanical corneal response to an air pulse pressure varies linearly with IOP. Figure 2.7 and Figure 2.8 illustrate that the right combination of corneal stiffness and IOP may result in the same maximal corneal deformation. Depending on the stiffness of the corneal tissue (characterized by a different set of material model parameters) and the IOP of the examined eye, an overlapping zone could exist. Therefore, it is not possible to distinguish between individual effects (IOP and material stiffness) without knowing the characteristic of one of them a priori, e.g. Cornea’s stiffness. As shown in Figure 2.9, the apex displacement during a non-contact tonometry showed a cubic relationship with corneal thickness. For a corneal thickness within the physiological range (500 – 600 microns), the maximal corneal displacement ranged withing the reported clinical range (0.7 – 1.3 mm). However, as the thickness decreases below 500 microns, the maximal corneal displacement increases rapidly. These corneal response at low CCT values could
correspond to an extreme LASIK intervention or an advanced ectasia (e.g. Keratoconus disease) in which the local corneal thinning could lead to a larger apical displacement as compared to healthy patients presenting a regular and smooth pachymetry. It should also be pointed out that, when the cornea is under the action of the IOP, the state of stress of the cornea corresponds to a pure traction membrane state, which means that the full cornea works in tension when it is subjected to its physiological IOP (i.e. no bending effects exists and it behaves as expected according to the shells and laminates theory), as shown in Figure 2.11. However, during air puff, the cornea experiences bending and, therefore, the anterior surface goes from a traction state of stress to a compression state of stress whereas the posterior surface works in tension (see Figure 2.11). This implies that collagen fibers in the anterior surface do not contribute to load bearing during the total duration of the air-puff, relying in this cases on the mechanical properties of the matrix. This non-physiological situation implies that the biomechanical characterization using an air pulse pressure loading accounts for the contribution of the collagen fibers only partially (only the posterior part of the cornea), contrary to the case of an inflation test where the cornea works under tension all the time. Therefore, the mechanical response characterized by non-contact tonometry represents a combination of the mechanical behavior of the cornea under traction (associate with the collagen fiber network) and, but not less important, the mechanical behavior under compression of the stroma. This is important since the state of the art mechanical testing of the cornea accounts for the mechanical response under tension only.\textsuperscript{31} In addition to the corneal stiffness and IOP, the clinical study by Huseynova et al.\textsuperscript{32} reported the CCT as another parameter with significant influence on the corneal response analyzed by non-contact tonometry using the CorVis ST system. In particular, these authors found significant differences in the firstplanation time and radius of curvature at highest concavity between central corneal thickness subgroups for each IOPcc group that was studied ($p < 1e^{-4}$). Numerical results from our study also suggest this. Our results show a cubic relationship between the maximum apical displacement and the corneal thickness. This cubic dependence obeys to the bending deformation induced in the cornea during the action of the air-pulse, as expected in a thin shell subjected to bending. This cubic dependency helps to explain the increment in corneal displacement on patients that have undergone LASIK surgery and whose cornea has suffered a significant reduction of thickness and curvature. A similar situation is found in patients with narrow diseased corneas affected by ectasia. Hence, the corneal response to an air puff is influenced by the mechanical properties of the cornea, the IOP, and topology (i.e., CCT and curvature). Therefore, analysis based on the evaluation of corneal response to an air pulse pressure, provides a response of the combined contribution of these effects, without being able to uncouple the precise contribution of each
factor. By this, the corneal mechanical properties cannot be assumed to be directly related to the parameters defining the corneal response to the air pulse. This fact has been also demonstrated by Glass et al. who have developed and validated a viscoelastic model to illustrate how changing viscosity and elasticity may affect corneal hysteresis (CH), concluding that low CH could be associated with either high elasticity or low elasticity, depending on the viscosity. A final comment is devoted to the limitation of this study. Corneal material has been assumed as hyperelastic, neglecting the intrinsic viscoelastic behavior of the tissue. However, since we were only interested in the maximum apex displacement, attained during the pressure rising phase of the air puff, and taking into account that a very fast load will result on an almost pure elastic response, it can be assumed that neglecting a corneal viscoelastic behavior would not significantly affect the results of study. Viscoelasticity may, however, have significant importance on the relaxation phase of the cornea after the air-puff stops. In addition, the study shows only results on one patient, and therefore, statistics regarding the influence of the patient specific eye geometry and IOP has not been computed yet. We are currently applying the presented in silico methodology to a larger set of healthy and pathological patients in order to determine the impact of patient-to-patient geometric variability and IOP on maximum corneal displacements and other proposed mechanical biomarkers. In conclusion, the proposed in silico methodology allows computing a sensitivity analysis of the mechanical properties of the corneal tissue, the IOP and the geometry of the cornea on the corneal deformation of patient specific geometric eye models. This type of analysis is not possible with standard non-contact tonometry devices since it has been demonstrated that they measure the combined contribution of all these factors on the corneal response. Thus, a cornea with high stiffness and low IOP may show the same deformation response as a cornea with low stiffness and high IOP. In addition, systems based on non-contact tonometry for characterizing the corneal biomechanics evaluates the mechanical response of the cornea under bending, whereas the corneal response to variations of the IOP depends on a pure membrane behavior of the cornea, a condition that is only achieved in biaxial or inflation loading. These results indicate that a complete in vivo corneal mechanical characterization would require more than one test in order to determine the membrane and bending behavior of the cornea independently.
This chapter describes the numerical algorithm capable of reconstructing patient-specific geometries, and simulating non-contact tonometry tests automatically.

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3.1 Introduction

The corneal shape is the result of the equilibrium between its mechanical stiffness (related to the corneal geometry and the intrinsic stiffness of the corneal tissue), intraocular pressure (IOP) and the external forces acting upon it such as an external pressure. An imbalance between these parameters, e.g. an increment of IOP (glaucoma), a decrement of the corneal thickness induced by refractive surgery or by a corneal material weakening due to a disruption of collagen fibers (keratoconus), can produce ocular pathologies (ectasias) which seriously affect patient’s sight. Consequently, it is important to understand how ocular factors such as IOP, geometry and corneal material are related to pathologies in order to improve treatments. The first step in this direction consists of the correct measurement of the IOP and corneal topography. To date, the IOP is measured by either contact tonometers (e.g. Goldmann Applanation Tonometry) or non–contact tonometers, e.g. CorVis ST (Oculus Optikgeräte GmbH), whereas the corneal topography is obtained with corneal topographers, e.g. Pentacam (Oculus Optikgeräte GmbH) and Sirius (Schwind eye-tech-solutions GmbH & Co.KG), which have reached a high level of sophistication and accuracy.

The availability of high resolution topographical data and the patient’s IOP have made possible to reconstruct a patient’s specific geometric model of the cornea, which makes it possible to study specific treatments and pathologies. In this regard, some patient–specific corneal models have already been reported in the literature. However, the pipeline described in these studies cannot be automated in a straightforward manner as to permit personalized analysis on large populations. Another limitation is that these methodologies rely on an approximation of the topographical data when building the corneal model. Studer et al. used Zernike polynomials to generate anterior and posterior corneal surfaces by approximating the available topographical data instead of directly incorporating the corneal thickness and curvature provided by the topographer. In addition, these numerical models did not provide an appropriate mesh convergence analysis so as to check the accuracy of the results.

An accurate numerical model of the eye is based on the identification of an adequate strain energy function from which the stress–strain relationship of the cornea is obtained. To achieve it, an understanding of the underlying structure of the tissue is needed. The cornea is composed of four different layers: epithelium, bowman’s membrane, stroma and endothelium. The stroma represents the major part of the cornea and is formed by different orthogonally crossed lamellae, which are made of collagen fibers. The corneal collagen is organized in two preferential directions: i) Nasal–Temporal direction, and ii) Superior–Inferior direction. On the contrary, limbus collagen fibers are disposed circumferentially. These characteristics provide

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2 Ruiseñor Vázquez et al. 2014, Ogbuehi and Osuagwu 2014
3 Hong et al. 2013
4 Bourges et al. 2009
5 Roy and Dupps Jr 2011, Studer et al. 2013
6 Studer et al. 2013
7 Lanchares et al. 2008, Newton and Meek 1998, Meek and Boote 2009
the cornea with a highly anisotropic behavior in addition to a nearly incompressible response.\(^9\) Even though the cornea shows an intrinsic viscoelastic behavior, for most applications it may be described as a nonlinear anisotropic hyperelastic solid.\(^10\) Additionally to these considerations on the mechanical response, it should be noticed that topographers measure the deformed geometry of the cornea under the action of the IOP but the stress and strain fields still remain unknown. Therefore, it is necessary to obtain a free–stress configuration of the eyeball that faithfully represents the load free configuration of the cornea. Elsheikh et al.\(^{11}\) and Roy et al.\(^{12}\) proposed an iterative geometric algorithm by varying IOP in order to obtain the reference eyeball geometry, whereas Studer et al.\(^{13}\) and Lanchares et al.\(^{14}\) proposed a pre-stressing algorithm based on the deformation gradient. However, these algorithms did not incorporate a consistent mapping of the direction of the collagen fibers onto the identified load free configuration (zero–pressure configuration). Riveros et al.\(^{15}\) have proposed a general pullback algorithm for nonlinear anisotropic materials in which the direction of collagen fibers are consistently mapped onto the identified zero–pressure configuration, which has already been applied to vascular geometries.

The aim of this work is to develop a robust methodology to incorporate a patient’s specific corneal topology into a finite element (FE) model of the eyeball, accounting for the free–stress configuration of the eyeball, and taking into account the hyperelastic anisotropic material response of the corneal tissue. Furthermore, the proposed pipeline is demonstrated on a set of 130 patients (53 healthy, 63 keratoconic and 14 post–LASIK eyes) following a general non–commercial non–contact tonometry protocol. Despite the use of an air-puff diagnostic test to validate the methodology, other types of test (i.e. inflation test or different surgical interventions) could be easily implemented and simulated. Finally, several results are addressed such as: the search for the most influential parameters on the numerical model by means of a sensitivity analysis based on the Design of Experiments theory\(^{16}\) (\(2^k\) full factorial and ANOVA analysis), the effect of the zero–pressure configuration on the model behavior and, to conclude, the comparison of the numerical results (displacements) with previous data reported in the literature from simulation\(^{17}\) and clinical studies.\(^{18}\)

### 3.2 Material And Methods

For a better comprehension and follow-up, the section is organized as the proposed pipeline for the patient–specific corneal modeling (see in Figure 3.1), from the topographical imaging acquisition to the desired FE simulation. The framework comprises five main steps namely: i) Step–1: Topographic Data Acquisition (sec. 3.2), ii) Step–2: Corneal Surface Reconstruction (sec. 3.2) , iii) Step–3: Numerical

\(^9\) Bryant and McDonnell 1996


\(^11\) Elsheikh et al. 2013

\(^12\) Roy and Dupps Jr 2011

\(^13\) Studer et al. 2013

\(^14\) Lanchares et al. 2008

\(^15\) Riveros et al. 2013

\(^16\) Montgomery 2002

\(^17\) Kling et al. 2014b

\(^18\) Roberts 2012, Hassan et al. 2014
Step-1: Topographic Data Acquisition

Clinical data from patients were collected prospectively, i.e. an ongoing measuring process without posterior revision of the patient's medical history, at the Department of Ophthalmology (OFTALMAR) of the Vithas Medimar International Hospital (Alicante, Spain). A comprehensive ophthalmologic examination was performed in all cases including: LogMAR uncorrected distance visual acuity (UDVA), LogMAR corrected distance visual acuity (CDVA), manifest refraction (sphere and cylinder), slit-lamp biomicroscopy, Goldmann tonometry, fundus evaluation, and corneal and anterior segment analysis by means of a Scheimpflug photography-based topography system, the Pentacam system version 1.14r01 (Oculus Optikgeräte GmbH, Germany). The patients wearing contact lenses for the correction of the refractive error were instructed in all cases to discontinue the use of contact lenses for at least 2 weeks before each examination for soft contact lenses and at least 4 weeks before each examination for rigid gas permeable contact lenses. All volunteers were adequately informed and signed a consent form before the inclusion in the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committee of the University of Alicante (Alicante, Spain). Inclusion criteria
were healthy eyes, eyes with the diagnosis of keratoconus according to the Rabinowitz criteria,\textsuperscript{19} or eyes that had undergone previous laser in situ keratomileusis (post-LASIK) for the correction of myopia (range, -0.50 to -8.00 D). Exclusion criteria were patients with active ocular diseases or patients with other types of previous ocular surgeries.

The Oculus Pentacam is a noninvasive system for measuring and characterizing the anterior segment using a rotating Scheimpflug camera which generates Scheimpflug images in three dimensions, with a dot matrix fine-meshed in the center due to the rotation. The full process takes a maximum of 2 seconds to generate a complete image of the anterior eye segment. A second camera detects any movement artefact (e.g. eye movement) so as to correct feasible measuring setbacks. The Pentacam calculates a 3-dimensional topographical model of the anterior eye segment using as many as 25,000 true elevation points. The images taken during the examination are digitalized in the main unit and transferred to a computer and analyzed in detail.

Gathered Pentacam corneal topographies (data from other topographers such as Sirius can also be handled) are represented as point cloud surfaces in the form of two 141x141 matrices. The first matrix contains the coordinates \((x, y, z)\) of the anterior corneal surface, whereas the second matrix represents the available pachymetry (corneal thickness) data at each \((x, y)\) point. Since pachymetry data are sometimes not available at all points in the anterior surface point cloud, the number of non-zero elements in the pachymetry matrix determines the total number of available data points for surface reconstruction. The posterior surface is the result of a point-to-point subtraction between the anterior surface and the pachymetry data.

\textit{Step-2: Corneal Surface Reconstruction}

A reliable patient-specific FE model of the cornea must incorporate patient's topographical data as much as possible. In this regard, the proposed framework makes use of actual patient's data where available, minimizing the amount of extrapolated data required to build a full three-dimensional FE model amenable for numerical simulations. Current topographers provide topographical data limited to a corneal area between 8 to 9 mm in diameter due to patient misalignment, blinking or eyelid aperture (see Fig. 3.2.a). However, a corneal diameter of 12 mm (average human size) is needed to build a 3D FE model.\textsuperscript{20}

In order to overcome this limitation, a surface continuation algorithm is proposed. Data extrapolation is performed by means of a quadric surface (see Appendix D.2)
Patient-specific Geometry

given in matrix notation as

\[ x^T A x + 2B^T x + c = 0, \]  

(3.1)

where \( A \) is a \( 3 \times 3 \) constant matrix, \( B \) is a \( 3 \times 1 \) constant vector, and \( c \) is an scalar, which define the parameters of the surface. Equation (3.1) is fitted to the topographical data by means of a nonlinear regression analysis.

Figure 3.2: Corneal surface reconstruction (Extreme post–LASIK eye used as example). (a) Projection of the 12 mm diameter corneal surface in the optical axis plane. Grey and blue shaded surfaces correspond to the corneal surface measured by the topographer (image–based geometry). Green area corresponds to the extended surface required in order to achieve a 12 mm diameter (approximating surface); (b) Surface smoothing at the joint between the extended surface and the patient’s corneal surface; (c) Contour map of the error between the point cloud data prior and after smoothing (less than a 5% at the corneal periphery).

To extend the corneal surface, the quadric surface, Eq. (3.1) should properly approximate the periphery of the patient’s topographical data (blue area in Fig. 3.2.a). For this reason and before fitting the Eq.(3.1), the central corneal part is removed using a level set algorithm based on the relative elevation of each corneal point with respect to the apex. In brief, starting at a relative elevation of 1, i.e., the apex, and reducing in steps of 0.005, subsequent level sets are identified (see gray area in Fig. 3.2.a). When the size of the level set, i.e., radius of the circumscribe circle, changes by less than a 15% between two consecutive increments, the algorithm stops. Corneal periphery is then obtained by subtracting the identified level set from the topographic data (blue area in Fig. 3.2.a).

When using an analytical surface as Eq. (3.1) to extend the corneal surface, there will always be a jump at the joint between the approximating surface and the point...
Methods for Characterising Patient-Specific Corneal Biomechanics

cloud surface (see Fig. 3.2.b). This discontinuity in the normal of the surface may lead to convergence problems or to non-realistic stress distributions on the cornea during the FE analysis. Hence, a smoothing algorithm based on the continuity of the normal between the quadric surface and the point cloud data is applied as shown in Fig. 3.2.b, producing local alterations in the patient’s topographic data near the border. However, these alterations are very small (less than a 3%) as outlined in the contour map of the error between the topographic point cloud data prior and after smoothing (Fig. 3.2.c), where the depicted data corresponds to an extreme post-LASIK patient (also used for testing the performance of the corneal surface reconstruction algorithm, see Figure 3.3.c).

The performance of the corneal reconstruction algorithm was demonstrated on three extreme cases: i) a healthy right cornea of a 50-year woman, with an apex pachymetry of 593 microns, a minimum pachymetry of 586 microns, a nasal–temporal radius of 7.63 mm and a superior–inferior radius of 7.79 mm; ii) a left cornea of a 60-year man affected by a keratoconus (KTC), with an apex pachymetry and a minimum pachymetry of 499 microns, a nasal–temporal radius of 6.87 mm and a superior–inferior radius of 7.69 mm; and iii) a post-LASIK refractive surgery, which is the right cornea of a 60-year woman, with an apex pachymetry of 379 microns, a minimum pachymetry of 375 microns (a particularly extreme case due to the large reduction in pachymetry after surgery), a nasal–temporal radius of 11.69 mm and a superior–inferior radius of 11.24 mm. In all cases, topographical data was acquired using a Pentacam topographer.

The approximation error obtained with the quadric surface and a traditional sphere

![Figure 3.3: Subtraction Error](image-url)

The approximation error obtained with the quadric surface and a traditional sphere
approximation with respect to the real surface, i.e. the subtraction error between the theoretical approximating surface and the real surface provided by the topographer, is shown in Figure 3.3 for the three considered extreme ocular geometries. For the Healthy eye, the sphere fits the corneal apex better than the corneal borders (in terms of the lowest difference between the real topographic surface and the approximating surface) with an error difference ranging from 33.6 to -74.4 microns (Figure 3.3.a top panel), whereas the quadric surface fits the corneal periphery better than the corneal apex with an error difference ranging from 21.5 to -30.3 microns (Figure 3.3.a bottom panel). Considering the KTC eye, the sphere fits the corneal center (excepts at the KTC location) better than the corneal borders with an error difference ranging from 49.9 to -102.2 microns (Figure 3.3.b top panel), whereas the quadric fits the corneal periphery better than the corneal center, where the pathology is very underestimated, with an error difference ranging from 180.1 to -57.1 microns (Figure 3.3.b bottom panel). Regarding the post–LASIK eye, the sphere fits the corneal center (excepts at the location of the surgery) better than the corneal borders with an error difference ranging from 71 to -47.4 microns (Figure 3.3.c top panel), whereas the quadric fits the corneal periphery better than the center of the cornea with an error difference ranging from 65.2 to -36.7 microns (Figure 3.3.c bottom panel). These results indicate that a sphere surface fits better at the center of the cornea while a quadric surface fits better at the periphery of the cornea (always in terms of the lowest difference between the real topographic surface and the approximating surface).

Table 3.1: Mean and Standard Deviation of the quadric surface coefficients sorted by population.

<table>
<thead>
<tr>
<th>Population</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>-0.1275</td>
<td>-0.1310</td>
<td>-0.0771</td>
<td>-0.0001</td>
<td>-0.0001</td>
<td>0.0022</td>
<td>0.0002</td>
<td>-0.0066</td>
<td>0.9212</td>
</tr>
<tr>
<td>Std</td>
<td>0.0092</td>
<td>0.0098</td>
<td>0.0158</td>
<td>0.0012</td>
<td>0.0037</td>
<td>0.0025</td>
<td>0.0083</td>
<td>0.0038</td>
<td>0.0504</td>
</tr>
<tr>
<td>KTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.1476</td>
<td>-0.1566</td>
<td>-0.0501</td>
<td>0.0003</td>
<td>0.0009</td>
<td>0.0194</td>
<td>-0.0016</td>
<td>-0.0062</td>
<td>0.9776</td>
</tr>
<tr>
<td>Std</td>
<td>0.0334</td>
<td>0.0351</td>
<td>0.0676</td>
<td>0.0038</td>
<td>0.0132</td>
<td>0.0179</td>
<td>0.0130</td>
<td>0.0173</td>
<td>0.0986</td>
</tr>
<tr>
<td>Lasik</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.1405</td>
<td>-0.1457</td>
<td>-0.0917</td>
<td>0.0004</td>
<td>0.0016</td>
<td>0.0008</td>
<td>-0.0062</td>
<td>-0.0044</td>
<td>1.0124</td>
</tr>
<tr>
<td>Std</td>
<td>0.0173</td>
<td>0.0188</td>
<td>0.0326</td>
<td>0.0016</td>
<td>0.0034</td>
<td>0.0036</td>
<td>0.0096</td>
<td>0.0063</td>
<td>0.1079</td>
</tr>
</tbody>
</table>

Therefore, the quadric surface model is better suited to extend the cornea to 12 mm in diameter as required by the FE model. Furthermore, regarding the surface fitting, the mean and the standard deviation of the quadric surface coefficients for the entire population (53 healthy, 63 keratoconic and 14 post–LASIK surgery) have been analyzed to observe the correctness of the numerical fitting on reproducing the corneal surface there where the topographer is unable to measure (see in Table 3.1). The coefficients associated with the quadratic terms clearly dominate indicat-
ing that the cornea is well approximated by an oblate spheroid (Note that "a" is very similar to "b" whereas "c" is a smaller order of magnitude). Hence, these results are consistent with the geometry of the cornea.

**Step–3: Numerical Model of the Cornea**

**Material Description**

Since the cornea is considered an anisotropic hyperelastic material, Gasser-Holzapfel-Ogden strain energy function (G–H–O)\(^{21}\) is proposed to describe its constitutive behavior.

\[
\psi_C = \frac{1}{D} \cdot \left( J_{el}^2 - \frac{1}{2} - \ln(J_{el}) \right) + C_{10} \cdot (I_1 - 3) + \frac{k_1}{2 \cdot k_2} \cdot \sum_{\alpha=1}^{N} \{ \exp[k_2(\bar{E}_\alpha)^2] - 1 \}
\]

\[
\bar{E}_\alpha \overset{\text{def}}{=} \kappa \cdot (I_1 - 3) + (1 - 3\kappa) \cdot (I_{4(\alpha\alpha)} - 1),
\]

where \(I_1\) is the first invariant of the modified right Cauchy-Green tensor \(\bar{C} = J_{el}^{-2/3}C\), \(J_{el}\) is the elastic volume ratio, \(I_{4(\alpha\alpha)}\) is a pseudo-invariant that represents the square of the stretch along the direction of the \(\alpha\)\(^{th}\) family of collagen fibers, being \(N\) the total number of families of collagen fibers (two for the human cornea). \(D\) represents the inverse of the volumetric modulus. The dispersion parameter, \(\kappa\), \((0 \leq \kappa \leq \frac{1}{3})\) determines the anisotropic grade: \(\kappa = 0\) implies transversely isotropy, and \(\kappa = 3\) implies isotropy. In addition, Eq. (3.2) assumes that collagen fibers only work under traction, i.e. \(\bar{E}_\alpha > 0\).

The material constants concerning the corneal and limbal constitutive model were obtained by means of non-linear regression analysis of a typical IOP–apical rise curve:\(^{22}\) \(C_{10} = 0.05 \text{ [MPa]}, D = 0.0 \text{ [MPa}^{-1}], k_1 = 130.9 \text{ [MPa]}, k_2 = 2490.0 \text{ [}\right)\) and \(\kappa = 0.33329 \text{ []}\). For the computations, the same mechanical properties and dispersion parameter have been assumed for all families of fibers. Figures 3.4.a-b show the stress–stretch and IOP–apical rise curves predicted with the proposed material model and also demonstrate that the numerical predicted IOP–apical rise curve is within the reported human range\(^{23}\) (see in Fig. 3.4.b).

The sclera has been assumed as an isotropic hyperelastic material\(^{24}\) (Eq. (3.3)). The distribution of fibers within the sclera far from the optical nerve insertion do not seem to follow a preferential direction, showing a random pattern and, therefore, it is likely to present a more isotropic behavior near to its equatorial plane than an anisotropic behavior on the surroundings of the optical nerve.\(^{25}\) In addition, the cornea plays the main role in our simulation study, since it receives the air-jet impact, whereas the sclera plays a secondary role as a more natural non-restrictive

\(^{21}\) Gasser et al. 2006, Holzapfel et al. 2000

\(^{22}\) Ariza-Gracia et al. 2015, Whitford et al. 2015

\(^{23}\) Ariza-Gracia et al. 2015, Whitford et al. 2015

\(^{24}\) Eilaghi et al. 2010

\(^{25}\) Coudrillier et al. 2015
boundary condition for the cornea, much better than restraining nodal displace-
ments or imposing theoretical boundary conditions on the corneal periphery. Fur-
thermore, the scleral material has proved to be much stiffer than the corneal.

\[
\psi_Y = \sum_{i=1}^{3} \frac{1}{D_i} (I_{el} - 1)^2 i + \sum_{i=1}^{3} Y_{i0} \cdot (I_1 - 3)^i
\]  

(3.3)

with \( Y_{10} = 0.81 \) [MPa], \( Y_{20} = 56.05 \) [MPa], \( Y_{30} = 2332.26 \) [MPa], \( D_i = 0.0 \) [MPa⁻¹].

\[\psi_{\text{corr}} = \frac{\sigma}{\lambda} \]

Finite Element Model

Once the corneal surface fitting is completed, it is introduced in the three-dimensional model of the anterior half ocular globe, which accounts for three different parts: the cornea, the limbus and the sclera. Since only the cornea can be partially measured by a topographer and neither the sclera nor the limbus can be measured with this procedure, average parts are used instead. The sclera was assumed as a 25 mm in diameter sphere with a constant thickness of 1 mm, whereas the limbus is a ring linking both, the sclera and the cornea. The geometry has been meshed using hexahedral elements by means of an in-house C program as shown in Fig. 3.4.c.
thus allowing precise control of the mesh size, as well as generating meshes with trilinear (8-nodes) or quadratic (20-nodes) hexahedral elements. Pachymetry data measured with the topographer is accurately mapped onto the three-dimensional finite element model during mesh generation. Finally, the FE model of the eyeball is completed by defining the corneal fibers over the two preferential orientations (a nasal-temporal and superior-inferior directions) and one single circumferential orientation embedded in the limbus (Fig. 3.4.d).

Symmetry boundary conditions have been defined at the scleral equator (Π plane in Fig. 3.4.c), i.e. the base of the semi-sclera which does not account for the optical nerve insertion since it is not necessary for the present simulation, in such a way that the boundary nodes are allowed to move on the symmetry plane Π but not normal to the plane, resulting in a much less restrictive boundary condition than fixing all nodal degrees of freedom. In addition, the inner surface of the eyeball is subject to the actual patient’s IOP, which was previously measured by means of Goldmann applanation tonometry.

Figure 3.5: Mesh convergence analysis of the FE model. (a) Left panel: Temporal pressure profile applied on the center of the cornea to simulate a non–contact tonometry test. Solid black line represents the temporal profile used in the simulations (up to 15 ms only). Right panel: Spatial pressure profile applied on the cornea’s anterior surface obtained by means of a CFD simulation; (b) Relative change in the maximum apical displacement, \( U_n \), (blue lines) and the minimum principal stress, \( S_{\text{min}} \), in the cornea (green line) as a function of the number of degrees of freedom (D.O.F) in the mesh for trilinear elements (discontinuous line) and quadratic elements (continuous line). Results are normalized respect to the coarsest mesh (83,400 D.O.F).

Computation time and accuracy are both the most important parameters when conducting an FE analysis but, unfortunately, the higher the accuracy required, the
greater the computing time also required. In order to reach an optimal trade-off between both, a convergence analysis of the finite element mesh was performed based on the simulation of a general non-commercial non-contact tonometry test. Linear and quadratic elements were considered, varying the number of elements through the corneal thickness from 2 to 8 elements (4, 6, and 8 for linear elements, and 2, 3, 4, and 5 for quadratic elements), and the maximum element size from 0.3 mm to 0.2 mm. The maximum apical displacement and the minimum principal stress have been considered as monitor variables of the convergence analysis. Regarding the features of the FE simulation, the air-puff acting on the anterior corneal surface was assumed as a metered collimated air pulse with a peak pressure of 25 kPa (approx. 180 mmHg), the loading phase (first 15 ms) of the entire temporal pressure profile (total duration of 30 ms) was considered (see in Fig. 3.5.a, left panel) and, finally, the spatial distribution of the pressure over the cornea (see in Fig. 3.5.b, right panel) was defined by performing a CFD simulation over a single healthy average model with the commercial software ANSYS (ANSYS, Inc.), in order to obtain a more realistic pressure distribution. The complete FE analysis was performed using the commercial finite element software ABAQUS (Dassault Systemes Simulia Corp.).

Figure 3.5.b shows the relative change in the maximum apical displacement and minimum principal stress as a function of the mesh size (degrees of freedom – D.O.F.). Results in Fig. 3.5.b have been normalized with respect to those obtained for the coarsest mesh. In general, trilinear elements show a much slower rate of convergence as compared to quadratic elements, besides predicting slightly shorter apical displacements and larger stresses. In this regard, the maximum apical displacement and the minimum principal stress change by less than 0.05% and 5% respectively when using a mesh with more than 186,000 D.O.F (62,000 nodes) and quadratic elements. Another remarkable aspect of the convergence analysis concerns the computation time, since a model with 186,000 D.O.F composed of trilinear hexahedra takes about three times more computing time than the equivalent model meshed with quadratic elements (results not shown).

Based on the convergence analysis, the FE model is generated with quadratic hexahedra and 5 elements through the thickness (11 nodes), resulting in an eyeball with 62,276 nodes (186,828 degrees of freedom) and 13,425 quadratic elements.

**Step-4: Zero-Pressure Algorithm**

When an eye is measured by a topographer, the identified geometry belongs to a deformed configuration due to the effect of the IOP (hereafter referred to as the image-based geometry) but the corneal pre-stress is neglected. Hence, an accurate stress analysis of the cornea starts by identifying the initial state of stresses
due to the physiological IOP present on the image–based geometry, or equivalently, the actual geometry associated with the absence of IOP (hereafter referred to as the zero–pressure geometry) as shown in Fig. 3.6.a. Consequently, an iterative algorithm is used to find the zero–pressure configuration of the eye \(^\text{29}\) (see algorithm in Figure 3.6.b) that keeps the mesh connectivity unchanged and iteratively updates the nodal coordinates. Moreover, the local directions of anisotropy (orientation of collagen fibers) are also consistently pulled-back to the current zero–pressure configuration.

In Fig. 3.6, \(X_{\text{REF}}\) stands for the patient’s geometry reconstructed from the topographer’s data, where \(X\) represents a \(N_n \times 3\) matrix that stores the nodal coordinates of the finite element eyeball, with \(N_n\) the number of nodes in the FE mesh, i.e., 62,276 nodes; \(X_k\) is the zero–pressure configuration identified at iteration \(k\); and \(X_k^d\) is the deformed configuration obtained when inflating the zero–pressure configuration \(X_k\) at the IOP pressure. The iterative algorithm updates the zero–pressure geometry, \(X_k\), until the infinite norm of the nodal error between \(X_{\text{REF}}\) and \(X_k^d\) is less than a tolerance, \(TOL\). The algorithm is described as follows:

\textbf{Initialization:} fiber directions, \(M\) and \(N\), are defined in the reconstructed corneal geometry (image–based geometry). Tolerance \(TOL\) and maximum number of iterations \(itemax\) are defined, and counter \(k\) is initialized.

**Step i:** At the \((k+1)\)-th iteration an FE stress analysis is performed considering the zero–pressure configuration computed in the \(k\)-th iteration, \(X_k\), as the reference configuration yielding to the deformed configuration at \(k\)-th iteration, \(X_k^d\). Boundary conditions and IOP (IOP*) are applied as described in the previous section.

**Step ii:** The \((k+1)\)-th zero–pressure geometry is computed as \(X_{k+1} := X_k - (X_k^d - X_{\text{REF}})\).

**Step iii:** The fibers are consistently mapped onto the \(k\)-th zero–pressure geometry as \(M_{k+1} = (F^{k+1})^{-1}M\) and \(N_{k+1} = (F^{k+1})^{-1}N\), with the deformation gradient being \(F^{k+1} = \partial X_{\text{REF}} / \partial X_{k+1}\).

**Step iv:** The counter \(k\) is incremented.

**Step v:** The infinite error norm is computed and, if it is less than \(TOL\) or the number of iterations is greater than \(itemax\), the algorithm stops.

**Step–5: Computer Simulation and Sensitivity Analysis**

The pipeline (see in Fig. 3.1) has been implemented using a combination of the Matlab software (used for computing the geometrical reconstruction), the ABAQUS
**GIVEN**

$X_{\text{REF}}$, fibres direction $M$ and $N$, $\text{itemax}$, $\text{TOL}$

**INITIALIZE**

$k=0$, $X_{k} = X_{\text{REF}}$, $M_{k} = M$, $N_{k} = N$

**REPEAT**

i) FE Analysis: internal pressure ($IOP_{*}$)

$X_{k}^{d} \rightarrow \text{ABAQUS}(X_{k}, M_{k}, N_{k})$

$\mathbf{E}_{k} = X_{k}^{d} - X_{\text{REF}}$

$\epsilon_{k} = \|X_{k}^{d} - X_{\text{REF}}\|_{\infty}$

ii) Update zero-pressure geometry

$X_{k+1} = X_{k} - \mathbf{E}_{k}$

iii) Fibre pull–back (Cornea & Limbus)

Deformation Gradient $\mathbf{F}^{k+1} = \frac{\partial X_{\text{REF}}}{\partial X_{k+1}}$

$M_{k+1} = (\mathbf{F}^{k+1})^{-1} M$

$N_{k+1} = (\mathbf{F}^{k+1})^{-1} N$

iv) $k = k+1$

**UNTIL** OR($\epsilon_{k} \leq \text{TOL}$, $k > \text{itemax}$)

---

**Figure 3.6: Zero–pressure algorithm.** (a) Influence of the IOP in the corneal shape (dog’s cornea); (b) Zero–pressure algorithm accounting for the pull–back algorithm with a consistent mapping of the fibers onto the current unloaded state. (c) Iterative scheme of the algorithm.
software (responsible for solving the FE problem), and an in-house C program for meshing. As described previously, the methodology is modular and the resulting FE model could be used to perform different computer simulations as for instance: eye inflation, surgical interventions and non–contact tonometry test among others.

A sensitivity analysis of the main parameters governing the numerical response of the *in silico* model (displacement, $U_{Num}$) has been addressed in two key aspects: i) the influence of introducing a random perturbation on the cornea’s fiber orientation based on the human cornea’s collagen dispersion reported in the literature; ii) the influence of 5 parameters governing the mechanical response of the cornea: intraocular pressure – IOP, central corneal thickness – CCT and material parameters – $C_{10}$, $k_1$, $k_2$.

The effect of the dispersion of the collagen fibers in humans reported by Meek et al. is analyzed by introducing a random perturbation on the numerical fiber’s pattern about the main orientations (nasal–temporal and superior–inferior). A healthy normal eye with three different levels of IOP (8, 12 and 30 mmHg) and fiber dispersion (0, 5 and 10 degrees), that comprises the reported range, has been considered, resulting in 9 additional computations.

In addition, a screening of the influence of the main parameters involved in the numerical simulation (IOP, CCT and material parameters) has been performed by means of a $2^k$ full factorial design extending those reported previously, that takes into account $k$ different variables at 2 different levels (Low and High). Since it is a basic study, the parameter variation (see Table 3.2) was considered as follows: the IOP was considered to range on our extreme clinical values (8 and 30 mmHg) and the corneal material parameters were considered within a 50% of variation relative to the reference values for the conducted simulations. The geometry was based on a modification of a healthy eye (as used for analysis of the influence of the fiber dispersion) in which a constant thickening and thinning of the corneal thickness was applied to obtain different CCTs (this adaptation of the corneal thickness was performed by modifying the posterior corneal surface in order to preserve the anterior corneal curvature).

Hence, a full factorial analysis of 5 variables at 2 different levels was carried out, resulting in 32 additional simulations. Additionally, the study of the main effects of the parameters, the interaction among them and the analysis of variances (using a N-way ANOVA analysis) were derived from the full factorial analysis to determine the most influential parameters on the numerical displacement.

<table>
<thead>
<tr>
<th>Case</th>
<th>IOP (mmHg)</th>
<th>CCT (µm)</th>
<th>$C_{10}$ (MPa)</th>
<th>$k_1$ (MPa)</th>
<th>$k_2$ (–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>12</td>
<td>583</td>
<td>0.05</td>
<td>130.9</td>
<td>2490</td>
</tr>
<tr>
<td>Low</td>
<td>8</td>
<td>450</td>
<td>0.025</td>
<td>65.45</td>
<td>1245</td>
</tr>
<tr>
<td>High</td>
<td>30</td>
<td>680</td>
<td>0.075</td>
<td>196.35</td>
<td>3735</td>
</tr>
</tbody>
</table>

Table 3.2: Levels of parameter’s variation (Low and High) involved in the $2^k$ factorial design (IOP: intraocular pressure; CCT: central corneal thickness; material parameters: $C_{10}$, $k_1$ and $k_2$). Reference parameters used for the conducted simulations are also included.
Finally, to demonstrate the robustness and capabilities of the proposed methodology, a non-commercial non-contact tonometry test is simulated on a population of 130 eyes. Simulations based on the image-based geometry and simulations based on the zero-pressure geometry have been performed for a total of 260 finite element analysis. Statistical analyses were performed in Matlab R2012 v.8.0, and data are reported by their mean and standard deviation (mean ± SD), respectively. Statistical significance was tested with the two-sample Kolmogorov–Smirnov test, where a two-sided p-value of less than 0.05 determined significance.

### 3.3 Results

Results obtained with the proposed pipeline for the patient-specific corneal modeling are presented in this section. First, the entire pipeline is demonstrated when studying the effect of accounting for the zero-pressure configuration on the simulation by testing the three sample cases used for checking the performance of the corneal reconstruction algorithm (sec. 3.2, Figure 3.3). Second, results regarding the sensitivity analysis are presented and, finally, the study is further and automatically extended to a larger population of 130 patients considering both the zero-pressure configuration and the image-based configuration.

### Effect of the Zero-Pressure Configuration

To check the influence of the zero-pressure configuration on the numerical simulation of the eye mechanics, the general non-contact tonometry test has been simulated as described in the Material and Methods section. The maximum and the time evolution of the apical displacement have been computed for three different levels of IOP (10, 19, and 28 mmHg), for the three geometric models described in the previous section (see in Fig. 3.3). Hence, each geometry was subjected to the procedure shown in Fig. 3.1 for each IOP value.

Figure 3.7 shows the apical displacement of the healthy eye for the three different levels of IOP, obtained with the zero–pressure model and the image–based model. Incorporating the initial stress of the cornea results in a stiffer corneal response to the air-puff (lower apical displacement), as evidenced in Fig. 3.7.b which shows that the initial pre-stress produces a shift in the maximum apical displacement vs. pressure curve. In addition, Fig. 3.7.a shows that the effect of the initial stress is more noticeable as the pressure of the air-puff increases as demonstrated by the divergence in the apical displacement time course between the two models (image–based geometry and zero–pressure geometry), from the moment in which the deformation of the cornea becomes significant to the maximum difference when the air-puff reaches its maximum pressure ($t = 15$ ms). Note also that the diver-

<table>
<thead>
<tr>
<th>IOP</th>
<th>Healthy</th>
<th>KTC</th>
<th>post-LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7.5</td>
<td>17.5</td>
<td>15.5</td>
</tr>
<tr>
<td>19</td>
<td>8.2</td>
<td>20.0</td>
<td>13.8</td>
</tr>
<tr>
<td>28</td>
<td>3.1</td>
<td>18.9</td>
<td>16.5</td>
</tr>
</tbody>
</table>
gence between the two curves initiates earlier for lower IOP values as shown in Fig 3.7a. This behavior shown in Fig. 3.7 is also observed in the KTC and post–LASIK geometries.

Table 3.3 shows the percentage of increase in the apical displacement due to the initial corneal pre-stress for different IOP and all geometries. The KTC model experiences the largest increment in apical displacement, whereas the Healthy model experiences the lowest increment in displacement. This result correlates well with the lower corneal pachymetry associated with the KTC and post–LASIK geometries.34

Figure 3.7: Effect of the initial stress in the healthy eye. (a) Evolution of the apical displacements for different IOP: i) zero-pressure model (discontinuous lines), and ii) image–based model (continuous line); (b) Maximum apical displacement for different IOP.

34 Ariza-Gracia et al. 2015
Sensitivity Analysis

Regarding the influence of the random perturbation of the collagen fibers orientation on the numerical displacement, the percentage difference in the corneal displacement ($\Delta U_{\text{apical}}$) among the models presenting random shift on the fibers and the original models with no dispersion is presented in the Table 3.4, showing that the maximum error does not exceed 0.03% in any combination. Hence, the influence of the fiber dispersion in the results is rather small.

The results of the 32 combinations for the $2^k$ full factorial analysis and the results of the N-way ANOVA analysis are presented in Table 3.5 and Table 3.6 respectively. The first primary results came from locally comparing the 12 experiments determined by Cotter's method,$^{35}$ i.e. comparing the minimum reference level (all parameters set to the low level, $-$, see in Table 3.5) with respect to the other 5 levels with all parameters set to the low level ($-$) except for the parameter under analysis which is set to the high level ($+$) and, vice versa, comparing the maximum reference level (all parameters set to the high level, $+$, see in Table 3.5) with respect to the other 5 levels with all parameters set to the high level ($+$) except for the parameter under analysis which is set to the low level ($-$). On the one hand, in terms of a local relative percentage difference in displacement with respect to the maximum displacement (Test 1, $U_{\text{Num}} = 2.563714$), those that seem to be the most influential parameters, since they show the highest relative decrement on displacement, are the IOP (Test 2, $-45.9\%$), the CCT (Test 3, $-50.0\%$) and the $k_1$ (Test 9, $-41.3\%$), whereas the least influential are $C_{10}$ (Test 5, $-9.9\%$) and $k_2$ (Test 17, $-7.6\%$). On the other hand, in terms of a local relative percentage difference in displacement with respect to the minimum displacement (Test 32, $U_{\text{Num}} = 0.547892$), those that seem to be the most influential parameters, since they show the highest relative increment on displacement, are the IOP (Test 31, $21.0\%$), the CCT (Test 30, $76.9\%$) and the $k_1$ (Test 24, $32.3\%$), whereas the least influential are $C_{10}$ (Test 28, $6.7\%$) and $k_2$ (Test 16, $0\%$).

A more complete analysis is achieved by observing the $p$-values and the F-statistic (F) of each Source (main effect of a parameter or interaction between different main parameters) presented in Table 3.6. According to these results, the IOP, CCT and $k_1$ are the most influential parameters on the numerical displacement ($U_{\text{Num}}$) since their F-statistics and their $p$-values are the highest, whereas $C_{10}$ presents a significant but low influence and $k_2$ is non-significant ($p$-value = 0.1609). Furthermore, the IOP–CCT interaction, IOP–$k_1$ interaction, and CCT–$k_1$ interaction seem to play a non-negligible role in the numerical response ($p$-values = 0.0). In addition, by analyzing the percentage of influence of each parameter in terms of its deviation with respect to its average value,$^{36}$ (Sum Sq. in Table 3.6), it can be highlighted that CCT, IOP, $k_1$, IOP–CCT and IOP–$k_1$ interactions represent more than the 95%

$^{35}$ Cotter 1979

$^{36}$ Montgomery 2002
Table 3.5: \(2^5\) full factorial design combinations \((2^5 = 32)\) and the resulting objective variable \(y\) (Numerical Displacement of the Corneal Apex, \(U_{N_{num}}\)) measured in millimetres.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>IOP</th>
<th>CCT</th>
<th>(C_{10})</th>
<th>(k_1)</th>
<th>(k_2)</th>
<th>(y - U_{N_{num}}) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.563714</td>
</tr>
<tr>
<td>Test 2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.386425</td>
</tr>
<tr>
<td>Test 3</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.152660</td>
</tr>
<tr>
<td>Test 4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.812387</td>
</tr>
<tr>
<td>Test 5</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2.307931</td>
</tr>
<tr>
<td>Test 6</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1.325756</td>
</tr>
<tr>
<td>Test 7</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.971684</td>
</tr>
<tr>
<td>Test 8</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.736133</td>
</tr>
<tr>
<td>Test 9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>1.504956</td>
</tr>
<tr>
<td>Test 10</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>1.037734</td>
</tr>
<tr>
<td>Test 11</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0.745937</td>
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<tr>
<td>Test 12</td>
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<td>+</td>
<td>-</td>
<td>+</td>
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<td>0.588232</td>
</tr>
<tr>
<td>Test 13</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>1.379099</td>
</tr>
<tr>
<td>Test 14</td>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0.985989</td>
</tr>
<tr>
<td>Test 15</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>0.667031</td>
</tr>
<tr>
<td>Test 16</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0.547892</td>
</tr>
<tr>
<td>Test 17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.368668</td>
</tr>
<tr>
<td>Test 18</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.343527</td>
</tr>
<tr>
<td>Test 19</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.114085</td>
</tr>
<tr>
<td>Test 20</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.796277</td>
</tr>
<tr>
<td>Test 21</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2.136569</td>
</tr>
<tr>
<td>Test 22</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1.284817</td>
</tr>
<tr>
<td>Test 23</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.947469</td>
</tr>
<tr>
<td>Test 24</td>
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<td>+</td>
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<td>-</td>
<td>-</td>
<td>0.724942</td>
</tr>
<tr>
<td>Test 25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>1.437088</td>
</tr>
<tr>
<td>Test 26</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>1.018412</td>
</tr>
<tr>
<td>Test 27</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>0.740186</td>
</tr>
<tr>
<td>Test 28</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>0.584746</td>
</tr>
<tr>
<td>Test 29</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>1.322432</td>
</tr>
<tr>
<td>Test 30</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.969044</td>
</tr>
<tr>
<td>Test 31</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0.663006</td>
</tr>
<tr>
<td>Test 32</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.545347</td>
</tr>
</tbody>
</table>
of the influence on $U_{Num}$, whereas $C_{10}$ represents less than 1% influence (see Pareto’s diagram in Figure 3.8.a and the pie chart in Figure 3.8.b).

The main effect of the present parameters on $U_{Num}$ is further depicted in Figure 3.8.c, reinforcing the idea of the strong influence of CCT, IOP and $k_1$ on the numerical yield since they present a large range of variation and a pronounced inverse slope, i.e. the lower the level of the parameter, the higher the yield, whereas $C_{10}$ presents a less pronounced slope and $k_2$ shows an almost constant response. Moreover, the interaction between the most influential parameters (CCT, IOP and $k_1$) is depicted in Figure 3.8.d, since there are no crossings or changes in their trends, a full inverse correlation is demonstrated for all the involved parameters: the highest level of the parameter will lead to the lowest level of the numerical displacement and vice versa.

**Effect of the Zero–Pressure Configuration.  A Large Population Study**

To gain a better understanding on the effect of the zero–pressure configuration, and to demonstrate the potential of the proposed methodology, a population of 130 patients (53 healthy, 63 KTC and 14 post–LASIK eyes) was analyzed. Topographical data were acquired with a Pentacam topographer and the patient’s IOP with a Goldman’s Applanation Tonometer (C.S.O. Srl). In order to validate the methodology, results from the numerical simulation were compared with clinical results obtained with a CorVis ST system reported in the literature (60 Healthy and KTC eyes,37 and 52 post–LASIK eyes 30 days after surgery38). In addition to the apical

37 Roberts 2012  
38 Hassan et al. 2014
Figure 3.8: Sensitivity Analysis. (a) The cumulative percentage of contribution of the parameters on the numerical displacement (%). The most important parameters that describe the numerical response with a 95% of confidence are the central corneal thickness (CCT – 50%), the intraocular pressure (IOP – 19%) and the material parameter associated with the fiber strength ($k_1$ – 18%). In addition, the interactions among IOP, CCT and $k_1$ comprise a 10% of the influence on the numerical response; (b) The total contribution of the analyzed parameters to the numerical response ($C_{10}$ contributes less than a 1% and $k_2$ presents non-significative influence); (c) The Main Effects of the analyzed parameters on the numerical displacement (CCT, IOP and $k_1$) show a highest inverse influence (Low parameter's level results in the highest displacement and vice versa) whereas $C_{10}$ and $k_2$ presents almost a constant influence; (d) The Main Interaction Effects among the most influential parameters (CCT, IOP and $k_1$) show a high inverse correlation between all parameters, resulting on the highest displacement when the lowest effects are considered, whereas the lowest displacement is achieved when the highest effects are considered.
displacement, the minimum principal stress, \(\sigma_{\text{min}}^{\text{Apx}}\), and minimum principal stretch, \(\lambda_{\text{min}}^{\text{Apx}}\), at the apex of the anterior surface have been taken into account.

Table 3.7 shows the mean and standard deviation of the three biomarkers obtained for the three populations with the image–based model and the zero–pressure model. Clinical results for the maximum apical displacement from the literature are also shown for completeness. Although results of the apical displacement are within the range obtained in clinical studies, the apical displacements obtained with the zero–pressure configuration model underestimate the clinical results, whereas those obtained with the image–based model overestimate the maximum apical displacement. A two sample Kolmogorov–Smirnov test on the apical displacement have shown no significant differences between KTC–Healthy and post–LASIK–Healthy patient-specific Geometry. A two sample Kolmogorov–Smirnov test on the apical displacement have shown no significant differences (p-value > 0.05) between post–LASIK–KTC, but have shown significant differences between KTC–Healthy and post–LASIK–Healthy for both, the image–based and the zero–pressure models, in agreement with clinical results.39 The same results were found for the stress and stretch biomarkers. However, when comparing the results obtained with the zero–pressure model and the image–based model for the same biomarker, significant differences in all three biomarkers were only found for the Healthy eye, whereas for the KTC and post–LASIK eye, significant differences were only found for the maximum apical displacement.

<table>
<thead>
<tr>
<th>Numerical data</th>
<th>Healthy</th>
<th>KTC</th>
<th>post–LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex Pac. [(\mu m]]</td>
<td>553.8±36.2</td>
<td>472.1±69.3</td>
<td>501.1±53.9</td>
</tr>
<tr>
<td>IOP(_{\text{GAT}}) [mmHg]</td>
<td>13.5±2.2</td>
<td>12.3±2.6</td>
<td>11.6±1.6</td>
</tr>
<tr>
<td>Image–based model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td>Healthy</td>
<td>KTC</td>
<td>post–LASIK</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-----</td>
<td>------------</td>
</tr>
<tr>
<td>(U) [mm]</td>
<td>1.04±0.14</td>
<td>1.20±0.19</td>
<td>1.15±0.11</td>
</tr>
<tr>
<td>(\sigma_{\text{min}}^{\text{Apx}}) [MPa]</td>
<td>-0.476±0.075</td>
<td>-0.624±0.156</td>
<td>-0.556±0.078</td>
</tr>
<tr>
<td>(\lambda_{\text{min}}^{\text{Apx}}) [-]</td>
<td>0.959±0.002</td>
<td>0.955±0.003</td>
<td>0.957±0.002</td>
</tr>
<tr>
<td>Zero–pressure model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td>Healthy</td>
<td>KTC</td>
<td>post–LASIK</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-----</td>
<td>------------</td>
</tr>
<tr>
<td>(U) [mm]</td>
<td>0.93±0.11</td>
<td>1.07±0.17</td>
<td>1.03±0.10</td>
</tr>
<tr>
<td>(\sigma_{\text{min}}^{\text{Apx}}) [MPa]</td>
<td>-0.440±0.071</td>
<td>-0.573±0.138</td>
<td>-0.520±0.077</td>
</tr>
<tr>
<td>(\lambda_{\text{min}}^{\text{Apx}}) [-]</td>
<td>0.960±0.002</td>
<td>0.956±0.003</td>
<td>0.958±0.002</td>
</tr>
<tr>
<td>Clinical Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Data</td>
<td>Healthy</td>
<td>KTC</td>
<td>post–LASIK</td>
</tr>
<tr>
<td>Apex Pac. [(\mu m]]</td>
<td>520.0±25.0</td>
<td>475.0±38.0</td>
<td>524.0±63.2</td>
</tr>
<tr>
<td>IOP(_{\text{Corvis}}) [mmHg]</td>
<td>14.4±2.5</td>
<td>14.4±2.2</td>
<td>14.2±4.2</td>
</tr>
<tr>
<td>Biomarker</td>
<td>Healthy</td>
<td>KTC</td>
<td>post–LASIK</td>
</tr>
<tr>
<td>(U) [mm]</td>
<td>1.04±0.10</td>
<td>1.13±0.12</td>
<td>1.08±0.14</td>
</tr>
</tbody>
</table>

The effect of the zero–pressure configuration is better appreciated in Fig. 3.9 where the percentage difference between the biomarkers computed with the image–based model and the zero–pressure model during the air-puff are depicted (the zero–

39 Roberts 2012, Hassan et al. 2014
Methods for Characterising Patient–Specific Corneal Biomechanics

A larger dispersion is present in all biomarkers for the KTC cases in comparison with the Healthy and the post–LASIK populations. Furthermore, the stiffer response of the cornea due to the incorporation of the zero–pressure configuration is also demonstrated, as the average apical displacement is always smaller for the image–based model than for the zero–pressure model (positive percentage) at all instants during the air-puff. However, this effect becomes more relevant as the pressure of the air-puff increases (maximum at 15 ms in the figure), coinciding with the maximum deformation of the cornea, and when the nonlinear response of the material becomes noticeable.

![Figure 3.9: Percentage difference of the biomarkers between the image–based model and the zero–pressure model](image)

**Figure 3.9: Percentage difference of the biomarkers between the image–based model and the zero–pressure model** (blue line is the average response and red bars the dispersion) at each instant during the air-puff. First row corresponds to the Healthy population, second row to the KTC population, and third row the post–LASIK population. Left column corresponds to the apical displacement, $U$; Middle column to the minimum in-plane principal stress at the apex of the anterior surface of the cornea, $\sigma_{Apx}^{\text{min}}$; Right column to the minimum in-plane principal stretch at the apex of the anterior surface of the cornea, $\lambda_{Apx}^{\text{min}}$.

Table 3.8 summarizes the percentage difference in the biomarkers for the high concavity time ($t = 15$ ms). It is remarkable that the average percentage difference for each biomarker is very similar for the three populations, with a significant larger dispersion in the case of KTC eyes.
### Table 3.8: Difference in biomarkers (%) at the high concavity time ($t = 15$ ms) for the three populations, taking the zero–pressure model as reference. Results given as mean ± standard deviation.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Healthy</th>
<th>KTC</th>
<th>post–LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_{\text{apx}}^{\text{min}}$</td>
<td>8.358 ± 0.730</td>
<td>8.873 ± 3.442</td>
<td>7.194 ± 1.011</td>
</tr>
<tr>
<td>$\lambda_{\text{apx}}^{\text{min}}$</td>
<td>-0.084 ± 0.012</td>
<td>-0.075 ± 0.029</td>
<td>-0.072 ± 0.015</td>
</tr>
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</table>

#### 3.4 Discussion

A novel automatized methodology to generate an FE model by incorporating the patient–specific corneal topographic data and which is amenable for different numerical simulations is proposed. Contrary to previous methodologies, the proposed approach does not approximate the topographical data where it is known, increasing the fidelity of the reconstructed patient model (see Fig. 3.2.c). The implementation of the proposed pipeline using Matlab, ABAQUS and an in–house C–code takes about 90 minutes to complete on a single patient: approximately 30 minutes in the model construction phase, and about 60 minutes for the finite element simulation (non including the zero–pressure algorithm) in a conventional PC with 8 core processor and 8 GB RAM. A more optimized implementation of the pipeline could substantially reduce these times, making the proposed methodology feasible for clinical use as an aided–diagnosis tool.

Furthermore, the mesh convergence analysis has demonstrated the importance of the finite element mesh used in the computations, particularly when modeling a non–contact tonometry test for which the bending behavior of the cornea must be accurately captured. Therefore, linear (four nodes tetrahedra) or trilinear elements (eight nodes hexahedra) must be used carefully since these elements do not capture the bending behavior properly. A sufficiently large number of elements through the thickness must be used in order to achieve accurate results (see Fig. 3.5.b). In this regard, the best trade-off between numerical accuracy and computation time when modeling a non–contact tonometry test was obtained with 20–node quadratic elements and 5 elements through the corneal thickness (186,828 D.O.F.).

Results derived from the sensitivity analysis can be assumed to represent the general numerical behavior of the entire population, despite only using a single healthy model, since the analyzed range of physiological parameters (IOP, CCT) covers the most extreme values of the corneal features belonging to the different population groups (the IOP ranges from 8 to 30 mmHg (glaucoma) and the CCT ranges from 450 microns (KTC) to 680 microns beyond the healthy range), whereas the material parameters were varied 50% with respect to the material selected for the conducted simulations ($C_{10}$ related to the ground matrix, $k_1$ related to the fiber strength over the stretch direction and $k_2$ which controls the fiber behavior under very large de-
formations). The CCT, whose contribution in the response perturbation is 50%, the IOP (19%) and the $k_1$ (18%) have been found to be the most influential parameters in the numerical displacement, whereas the remaining parameters ($C_{10}$ and $k_2$) seem to have a negligible contribution on the response variation (see Table 3.6 and Figure 3.8). Furthermore, these results are supported in physical terms since the thickness (CCT) follows an inverse cubic relationship with the displacement when a shell is subjected to bending.\textsuperscript{42} IOP represents a constant opposite force to external forces which greatly modifies the deformation amplitude of the corneal apex, and $k_1$ represents the fiber's resistance to stretching: the higher the stretching (deformation), the higher the contribution of the fibers. The ground matrix term ($C_{10}$) does not seem to play a major role in the numerical problem due to a two-fold reason: its contribution to the global stiffness is quite small and the global response of the cornea is governed by bending (see Figure 3.10). Finally, the $k_2$ would play a major role should the cornea reach higher intraocular pressures, however, the material response is dominated by the $k_1$ term in the physiological IOP range. Hence, the results of the sensitivity analysis along with the ANOVA analysis show a full inverse correlation among all the parameters and the numerical displacement and, in addition, further demonstrate that the apex displacement obeys an interplay among the geometry, the mechanical behavior of the cornea (material properties) and the intraocular pressure as has been previously reported.\textsuperscript{43}

The methodology has also been applied to evaluate, in a population of 130 patients (53 healthy eyes, 63 KTC eyes and 14 post–LASIK), the effect of the zero–pressure on the results of a general non–commercial non–contact tonometry simulation test. Numerical results were compared to reported clinical results obtained with a CorVis ST in order to validate the process, showing a good agreement between the numerical global response and the clinical tests. Additionally, our numerical results have been found to be in the same range as the numerical results reported by Kling et al.\textsuperscript{44} However, Kling et al. have used numerical models of porcine and human corneas that accounted for different boundary conditions and a material model which included a viscoelastic contribution. It is important to note that our simulation did not pretend to model a particular commercial device, but only to replicate a typical evaluation test. Hence, the main characteristics of the test such as the peak pressure of the air-puff, or the location and duration of the air pulse, were set in order to emulate a general non–contact tonometer. In addition, some assumptions were made regarding the air pressure over the cornea. Even though the pressure has been assumed to vary in time and space (see Fig. 3.5.a), shear effects on the corneal surface due to the air-puff has been neglected. Our results also indicate that the initial pre-stress of the cornea due to the IOP stiffens the corneal response, leading to significant differences in the apical displacement obtained with the zero–pressure model and the image–based model. Furthermore, results for the KTC
population showed a considerable larger dispersion as compared to the Healthy and the post–LASIK population, which correlates with the larger dispersion present in the pachymetry data for the KTC eyes.

This can also be related to the important effect of the corneal thickness on the corneal response when subjected to the action of an air-puff. In more detail, when subjected to an air-puff, the cornea passes from a pure tensile membrane state of stress due to the IOP, to a bending state of stress where the anterior surface experiences contraction while the posterior surface is in traction (see Fig. 3.10). Thus, the previous work presented in Ariza-Gracia et al. helps to explain the significant sensitivity of the results to changes in corneal pachymetry, this being subsequently demonstrated in the sensitivity analysis, since, as aforementioned, the bending stiffness follows an inverse cubic relationship with the corneal thickness.

In this line of results, the study conducted on Healthy, KTC and post–LASIK eyes gave values for the apical displacements within the range of clinical results even though all models have used the same corneal material. Therefore, this fact along with the present sensitivity analysis may suggest that the geometrical corneal features could be more important than the corneal tissue considerations when only the maximum bending apex displacement is studied.

Finally, although the proposed pull-back algorithm used to find the free–stress configuration of the eye is similar to other approaches previously proposed in the literature, the present methodology has the advantage of being the first to incorporate a consistent mapping of the collagen fibers onto the current zero–pressure configuration of the eye. In addition, the proposed algorithm found the zero–pressure geometry in less than 10 iterations with a tolerated relative error of less than 0.2 microns (less than a 0.05% of the corneal thickness).
the corneal response, our results also indicate that the proposed algorithm preserves the tissue volume globally, i.e. the zero-pressure and image-based geometries had the same volume (volume change less than 0.001%) and, moreover, the volume is also preserved locally with a maximum volume change of less than 0.3%. This is particularly important for three-dimensional solid simulations, since the cornea, the limbus and the sclera are considered incompressible materials. This feature of the algorithm is a consequence of using a quasi-incompressible material description for the different tissues, in addition to the nearly polar symmetry of eye that causes almost a radial deformation under the action of the IOP.

Last but not least, the study presents a number of limitations. The same material anisotropic properties for the cornea and the limbus for all patients have been considered, including neither the patient-specific material parameters nor the patient-specific collagen fibers pattern. However, to date, the only available human data in the literature is limited to pressure-apical rise curves on a small number of patients, providing only a range of mechanical response. For this reason, we have decided to use a set of parameters that fit a particular curve within the reported range as shown in Fig. 3.4.b, although accounting for the variability in the mechanical properties will certainly affect the variability in the biomarkers (Table 3.7), as further demonstrated in the sensitivity analysis (see Table 3.6 and Figure 3.8). Therefore, the main conclusions regarding the influence of the zero-pressure configuration on the simulation results will not be affected. Moreover, although a fixed general pattern of collagen fibers is used, the random perturbation of the collagen fibers following the results of Meek et al.,\textsuperscript{48} does not quantitatively affect the numerical displacement (a maximum of a 0.03% of variation, see Table 3.4). Finally, the material model could be improved by considering the viscoelastic behavior.\textsuperscript{49}

In conclusion, a novel \textit{in silico} methodology to generate an FE model that incorporates the patient-specific corneal geometry has been proposed. The pipeline allows \textit{in silico} tests to carry out a sensitivity analysis of the mechanical properties of the corneal tissue, the IOP, and the geometry of the cornea on the corneal deformation of patient-specific geometric eye models. This allows improved understanding of the eye biomechanics, as well as helping to plan surgeries, i.e., LASIK surgeries, or to interpret the results of new diagnosis tools, as in the case of non-contact tonometers. The proposed methodology could also be applied for performing inverse FE analysis on a patient-specific corneal model in order to identify the mechanical parameters on the patient’s cornea.

\textsuperscript{48} Meek and Boote 2009
\textsuperscript{49} Kling et al. 2014b
4

Patient-specific Material Prediction

Science is not, despite how it is often portrayed, about absolute truths. It is about developing an understanding of the world, making predictions, and then testing these predictions.

This chapter copes with the generation of a prediction model for the mechanical properties of the corneal tissue.

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4.1 Introduction

Corneal biomechanics is an open topic in ophthalmology. Precise knowledge about the underlying factors that affect the corneal mechanical response will allow establishing better clinical diagnoses, monitoring the progression of different diseases (e.g., keratoconus, a non-inflammatory disease that causes disruption of the collagen fibers) or designing a priori patient-specific surgical plans that may reduce the occurrence of unexpected outcomes.

Non-contact tonometry has recently gained interest as a diagnostic tool in ophthalmology and as an alternative method for characterizing the mechanical behavior of the cornea. In a non-contact tonometry test, a high-velocity air jet is applied to the cornea for a very short time (less than 30 ms), causing the cornea to deform, while the corneal motion is recorded by a high-speed camera. A number of biomarkers associated with the motion of the cornea, i.e., maximum corneal displacement and time between first and second applanations, among others, have been proposed to characterize pre- and post-operative biomechanical changes. However, this response is the result of the interplay between the geometry of the cornea, the intraocular pressure (IOP), and the mechanical behavior of the corneal tissue, as has been demonstrated by recent experimental and numerical studies. These studies suggest that this interplay could be the reason for some unexpected clinical results (i.e., a softer cornea with a higher IOP could show the same behavior as a stiffer cornea with a lower IOP). Although the geometry and the IOP can be measured using corneal topographers and Goldmann tonometry applanation tests (GATs), the mechanical behavior of the cornea cannot be directly characterized in vivo.

The human cornea is composed of an almost incompressible layered base material (matrix), mainly composed of water, where two families of orthogonal collagen fibers are embedded. Due to this structure, the tissue behaves as an anisotropic solid that has two preferential directions corresponding to the direction of the collagen fibers. A number of material models have been proposed to reproduce the behavior of the cornea, ranging from simply hyperelastic isotropic materials to more complex models coupling the hyperelastic isotropic response for the matrix (neo-Hookean models) with the anisotropic response of the collagen fibers of the eye. These material models have been incorporated into computer models of the eye to simulate surgical interventions and tonometry tests in an effort to demonstrate the potential of these in silico models.

However, numerical studies have found that the contribution of the fibers to load bearing during a tonometry test is highly reduced due to the bending mode of deformation imposed by the test. Under this particular loading condition, other factors such as the IOP or the central corneal thickness (CCT) were found to be more significant in the response of the cornea to the air puff. Moreover, in the physio-

3 Ariza-Gracia et al. 2015, Roberts 2014
4 Pinsky and Datye 1991, Pinsky et al. 2005
5 Lago et al. 2015
8 Ariza-Gracia et al. 2015, 2016b
logical range of IOP (from 10 to 15 mmHg) and CCT (from 500 to 600 microns), the corneal tissue is not subjected to large stresses, with the fibers bearing relatively low loads. In addition, experimental studies in porcine and human eyes have demonstrated that fibers play a major role only when the IOP increases to values above the physiological range. Therefore, it appears that the mechanical behavior of the matrix will play a significant role in reproducing the corneal response during a tonometry test. Furthermore, some authors have suggested that only one \textit{in vivo} technique may not be sufficiently accurate for properly characterizing the material properties, such as Kok et al. However, at present, it is the only clinical device that permits a non-invasive analysis of the human cornea, as biaxial or inflation tests can only be performed \textit{ex vivo}.

Over the past decade, with the development of large and extensive datasets, the use of artificial neural networks (ANNs) has returned to the spotlight. Essentially, an ANN intends to model the human brain by mathematically reproducing the neural architecture to learn and recognize patterns or to adjust functional responses. In ophthalmology, commercial topographers implement different types of ANNs to establish a classification between healthy eyes and diseased eyes (e.g., keratoconus eyes, KTC, or ectasias post-LASIK). Unfortunately, these ANNs are primarily based on the geometrical features of the cornea (e.g., radii, thickness, diopters, shape factors, and so forth), and it is not common to consider mechanical variables such as the intraocular pressure (IOP). In addition to ANNs, response surface methods have also been used in biomedical sciences for predicting the effects of different model parameters on a set of biomarkers associated with a particular pathology. The great interest in these mathematical methods relies on the immediateness of their response, which is a key factor for clinical applications. However, they suffer from an important weakness: the extension of the training dataset. These methods are based on precisely learning a considerable amount of data under different conditions to lead to a proper and accurate response of the system. Otherwise, a poor prediction or an overfitting in the solution could be reached with catastrophic results. Unfortunately, the higher the complexity of the applied neural network, the higher the number of cases that are needed for both training and validating the training. Therefore, this is a clear limiting factor when dealing with patient data. Apart from the aforementioned mathematical tools, another optimization approach has been used for determining the material properties of the human cornea: the inverse finite element method (henceforth IFEM). This method uses an iterative optimization procedure that changes a set of unknown parameters to match the numerical response with the experimental response. Thus, it requires a highly accurate definition of the problem and sufficiently reliable boundary conditions. Moreover, each case of interest must be evaluated ad hoc, resulting in a time-consuming process that is not real time and hence not interesting for real
Patient-specific Material Prediction

clinical applications.

The present work aims to construct predictors for real-time clinical applications based on ANN and quadratic response surface (QRS) approximations to obtain the parameters of the constitutive model of a patient’s cornea using 3 clinical biomarkers as inputs: the maximum corneal displacement measured during a non-contact tonometry test ($U_i$), the patient’s IOP, and geometrical features of the cornea. The predictive tool relies on a dataset generated by the results of finite element simulations of the non-contact tonometry test. The simulations are based on combinations of patients of a real clinical database (the patient-specific corneal geometry and the Goldmann IOP$^{15}$) and of corneal material properties of the numerical model to predict the corneal apical displacement. In brief, the finite element model is used to perform a Monte Carlo (MC) simulation in which the material parameters and the IOP are uniformly varied within an established range. The range for the material parameters was determined by considering the experimental results from an inflation test reported in the literature$^{16}$ and the physiological response of the cornea to an air-puff device (i.e., displacement of the cornea using a CorVis device). First, the inflation tests were used to initially screen the model parameters, to constrain the search space of the optimization and in an attempt to avoid an ill-posed solution.$^{17}$ Second, the range of each material parameter was then determined such that the in silico inflation curve was within the experimental window. In this way, both physiological behaviors of the cornea are simultaneously fulfilled: the response to an inflation test (biaxial stress) and the response to an air-puff test (bending stress). Subsequently, the generated dataset was used to implement different predictors for the mechanical properties of the patient’s corneal model in terms of variables that are identified in a standard non-contact tonometry test. Eventually, the resulting models were tested on five different, new and unknown patients to demonstrate the potential and soundness of the proposed methodology in terms of predicting corneal tissue properties.

4.2 Materials and Methods

Patient data

Topographical data of the cornea and IOP from 130 patients (53 healthy, 63 keratoconic and 14 post-LASIK surgery)$^{18}$ were collected prospectively, i.e., an ongoing measuring process without posterior revision of the patient’s medical history, at the Department of Ophthalmology (OFTALMAR) of the Vithas Medimar International Hospital (Alicante, Spain). A comprehensive ophthalmologic examination was performed in all cases, including Goldmann tonometry and analysis of the corneal anterior and posterior segments using a Scheimpflug photography-based topog-

$^{15}$ Ariza-Gracia et al. 2016b

$^{16}$ Whitford et al. 2015, Bryant and McDonnell 1996

$^{17}$ Kok et al. 2014

$^{18}$ Ariza-Gracia et al. 2015, 2016b
raphy system (Pentacam system, Oculus, Germany). The inclusion criteria were as follows: healthy eyes, eyes diagnosed with keratoconus according to the Rabinowitz criteria,¹⁹ and eyes that had undergone previous laser in situ keratomileusis (post-LASIK) for the correction of myopia (range -0.50 to -8.00 D). The exclusion criteria were patients with active ocular diseases or patients with other types of previous ocular surgeries. Clinical validation data were collected prospectively at the Qvision Ophthalmic Unit of the Vithas Virgen del Mar Hospital (Almeria, Spain). A comprehensive ophthalmologic examination was performed in all cases, including Goldmann tonometry, corneal and anterior segment analysis using a Scheimpflug photography-based topography system (Pentacam, Oculus, Germany) and corneal dynamics analysis (CorVis, Oculus, Germany). This study adhered to the guidelines of the Declaration of Helsinki and was approved by the ethics committee of the University of Alicante (Alicante, Spain).

Construction of the predictive model

Figure 4.1 shows the main steps of the proposed methodology. As stated in the introduction, the methodology relies on the use of a previously developed algorithm for the patient-specific geometrical reconstruction of the cornea and the simulation of a non-contact tonometry test.²⁰ To generate the dataset, two main steps

¹⁹ Rabinowitz 1998
²⁰ Ariza-Gracia et al. 2016b
have to be differentiated. In the first step, an initial screening over the constitutive model parameters is performed using the inflation experiments reported in the literature.\textsuperscript{21} There are two benefits associated with this step: constraining the space of solutions for the subsequent step and restraining the space of solutions to those that behave physiologically on the inflation range. The second step corresponds to the generation of the training dataset using a Monte Carlo analysis. The \textit{in silico} simulations of the non-contact tonometry test using the clinical patient-specific corneal topography and the clinical Goldmann IOP are used to obtain the bending behavior of the cornea. By filtering with the clinical ranges of maximum deformation amplitude,\textsuperscript{22} the space of material parameters that behave physiologically in both experiments (inflation and air puff) is obtained. Following the Monte Carlo simulation, an analysis of variance (ANOVA, using a second-order linear model for the sum of squares and accounting for the interaction between the parameters) is performed to identify the impact of the variables on the maximum displacement of the corneal apex, thereby defining the main inputs of the predictors. The resulting dataset is then used to train a set of 4 different predictors in terms of the material model parameters ($D_1$, $D_2$, $k_1$, and $k_2$) and the main variables identified through ANOVA. Finally, the predictors are tested with clinical results from a non-contact tonometry test on five patients to validate the methodology using unknown patient data.

**Finite Element Model**

The FE model consists of the patient-specific corneal geometric data, which are provided by the topographer, the limbus and half of the sclera.\textsuperscript{23} The geometry is meshed using quadratic hexahedral elements (62,276 nodes and 13,425 elements). The limbus and the cornea are considered to be anisotropic solids described by the same strain energy function but with different preferential directions (the cornea is assumed to be orthotropic with two orthogonal families of fibers, whereas the limbus is assumed to be transversely isotropic with only one family of fibers). The limbus is assumed to have the same material properties as the cornea since a proper \textit{in vivo} characterization has not yet been reported and because it is considered to be a more compliant boundary condition for the cornea far from the zone of influence of the air jet.\textsuperscript{24} Material models are described in detail in the following section. Conversely, the sclera is assumed to be an isotropic solid since the region of interest is far from the optic nerve insertion. Symmetry boundary conditions are defined on the scleral symmetry plane, and the intraocular pressure is assumed to be an equally distributed internal pressure determined by the Goldmann tonometry test.

To properly simulate the profile of pressure over the cornea of the non-contact tonometry test, a detailed description of the FE model is necessary.
tonometry from a purely structural perspective, a computational fluid dynamics simulation using ANSYS was conducted to determine the pressure pattern over the cornea due to the air puff. Although it is an approximation since the cornea is considered to be a rigid wall interface for the sake of the fluid analysis, a bell-shaped profile with a peak pressure set to 15 kPa is obtained (commercial devices range between 10 and 15 kPa), following a 30 ms temporal load profile provided by Oculus (only the load phase is considered). In addition, a zero-pressure algorithm is performed as a step prior to the air-puff simulation and is necessary for determining the corneal tissue pre-stress due to the IOP. Briefly, a fixed-point iterative optimization is applied, where an initial model of the eyeball is subjected to an internal pressure to deform. Subsequently, the error between the measured configuration (i.e., topographer geometry) and the deformed configuration is computed. If the error is greater than a tolerance, a new initial model is computed by subtracting the point-to-point error. Eventually, the algorithm stops once the measured reference is achieved when pressurizing the initial (usually smaller) model (for further details, see Ariza-Gracia et al. 2016b).

**Material Model**

The form of the strain energy function for modeling the cornea corresponds to a modified version of that proposed by Gasser–Holzapfel–Ogden for arterial tissue, where the neo-Hookean term has been substituted by an exponential term

$$\psi(C, n_\alpha) = D_1 \cdot \left\{ \exp[D_2 \cdot (I_1 - 3)] - 1 \right\} + \frac{k_1}{2} \cdot k_2 \cdot \sum_{\alpha=1}^{N} \left\{ \exp[k_2 \cdot (\tilde{E}_\alpha)^2] - 1 \right\} + K_0 \cdot \left( \frac{I_0^2}{2} - \ln(I_{el}) \right),$$

with $\tilde{E}_\alpha \overset{\text{def}}{=} \kappa \cdot (I_1 - 3) + (1 - 3\kappa) \cdot (I_{4(\alpha\alpha)} - 1)$,

(4.1)

where $C$ is the right Cauchy–Green tensor; $I_{el} = \sqrt{\det C}$ is the elastic volume ratio; $D_1$, $D_2$, $k_1$ and $k_2$ are material parameters; $K_0$ is the bulk modulus; $N$ is the number of families of fibers; $I_1$ is the first invariant of the modified right Cauchy–Green Tensor $\tilde{C} = I_{el}^{-2/3}C$; and $I_{4(\alpha\alpha)} = n_\alpha \cdot \tilde{C} \cdot n_\alpha$ is the square of the stretch along the fiber's direction $n_\alpha$. The parameter $\kappa$ describes the level of dispersion in the fiber's direction and has been assumed to be zero since it has been reported that a dispersion in the fibers of $\pm 10$ deg about the main direction results in a maximum variation of 0.03% on the maximum corneal displacement.

The strain-like term $\tilde{E}_\alpha$ in Eq. 4.1 characterizes the deformation of the family of fibers with preferred direction $n_\alpha$. The model assumes that collagen fibers bear load only in tension while they buckle under compressive loading. Hence, only
when the strain of the fibers is positive, i.e., $\tilde{E}_\alpha > 0$, do the fibers contribute in the strain energy function. This condition is enforced by the term $< \tilde{E}_\alpha >$, where the operator $< \cdot >$ stands for the Macauley bracket defined as $< x >= \frac{1}{2}(|x| + x)$. The model has been implemented in a UANISOHYPER user subroutine within the FE software Abaqus.

Due to the random distribution of fibers far from the optic nerve insertion, the sclera has been assumed to be an isotropic hyperelastic material $^{27}$ (Eq. 4.2).

$$\psi_Y = \sum_{i=1}^{3} K_i (J_{el} - 1)^{2i} + \sum_{i=1}^{3} C_{10} \cdot (I_1 - 3)^i,$$  

(4.2)

where $C_{10} = 810$ [kPa], $C_{20} = 56,050$ [kPa], $C_{30} = 2,332,260$ [kPa], and $K_i$ [kPa] is automatically set by the finite element solver during execution.

**Monte Carlo Simulation**

Due to the large dispersion in the corneal responses to inflation and air-puff tests and because the behavior of the fibers should not be properly characterized by a single experiment, the Monte Carlo simulation was conducted in two steps. First, the inflation experiments were used for screening the range of values of the material model that behaves physiologically in a biaxial stress state and hence constraining the searching space in subsequent steps. A total of 81 combinations of the material parameters were used to simulate an inflation test on an average healthy eye (see Figure 4.2b). The in silico inflation curves were then compared with experiments reported in the literature $^{28}$ and the range of material parameters leading to curves within the experimental window was determined. The identified range of parameters was set to $D_1 [kPa] \in (0.0492, 0.492)$, $D_2 [-] \in (70, 144)$, $k_1 [kPa] \in (15, 130)$, and $k_2 [-] \in (10, 1000)$.

The second step was to generate the dataset using the Monte Carlo simulation and considering a uniformly distributed sample of the material parameters within the previously identified range. A uniform distribution was assumed since there are no a priori data on the dispersion of the mechanical parameters in the human cornea, and therefore, total ignorance about the population is assumed. Otherwise, a bias could be introduced on the outcome of the system. Additionally, to account for the physiological diurnal variations in the IOP $^{29}$, variations in the IOP ranging from 8 to 30 mmHg along with the patient’s IOP at the moment of the examination were also considered in the Monte Carlo simulation. Hence, for each available geometry in the clinical database, 72 different samples of the material parameters and the IOP, uniformly distributed in their respective ranges, were used to conduct 72 simulations of the non-contact tonometry test. Consequently, a total of 9,360 computations (i.e., 72 combinations times 130 geometries) were scheduled. The
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generated dataset consisted of the following variables: classification (healthy, KTC and LASIK), computation exit status (failed or successful), material parameters ($D_1$, $D_2$, $k_1$ and $k_2$), IOP, CCT, nasal-temporal curvature ($R_h$), superior-inferior curvature ($R_v$) and the computed maximum displacement of the cornea ($U_{num}$).

After the dataset was generated, ANOVA was performed to identify the most influential model parameters (geometry, pressure and material) on the numerical displacement, $U_{num}$, obtained with the non-contact tonometry simulation. The results from this analysis were used to identify the geometric parameters to be included in the construction of the predictor functions for the material parameters. ANOVA was conducted on the global dataset without differentiation between the populations and for each of the populations (healthy, keratoconus or KTC, and LASIK). Since the dataset is randomly generated, ANOVA cannot be directly conducted on the data. Instead, a quadratic response surface was first fit to $U_{num}$ (e.g., $U_{num} = f(\text{geometry, pressure, material})$). Then, a Pareto analysis (i.e., it states the most influential parameters on an objective variable, arranging them in decreasing order by taking into account the cumulative sum of the influence until reaching a 95% variation on the objective variable) was used to determine the most influential parameters on the dependent variable, $U_{num}$.

The generated dataset was used to construct predictors for the mechanical properties of the patient's cornea in terms of variables that are measured with a standard non-contact tonometry test. Two different approaches were implemented (see Fig.4.1): i) response surface approach and ii) neighborhood-based approach.

**Response surface approach**

This approach is based on adjusting, or training, a predictor model for each material parameter ($D_1$, $D_2$, $k_1$ and $k_2$). Individual predictors were constructed using either an ANN or a quadratic response surface. For the ANN approach, two different mathematical models were considered: multiple layer perceptron, MLP, and support vector regressor, SVR. As an alternative to the ANN, a quadratic RS (QRS) was fit for each material parameter.

**Artificial Neural Network: Multiple Layer Perceptron (MLP).** An MLP is a feedforward ANN whose aim is to map a set of input variables (i.e., parameters that define the problem) into an output, allowing non-linear separable sets to be distinguished. It consists of different layers formed by 'neurons' or processing elements with non-linear activation: input layer, hidden layer and output layer. This technique is a supervised back-propagation learning technique for the training.\(^\text{30}\) For the present study, an ensemble of 7 independent MLPs has been configured, obtaining the output as the average of the individual outputs.

\(^{30}\) Van Der Malsburg 1986
(reducing the inherent variability of the method). Each independent MLP has been trained using a Levenberg-Marquardt minimization with early stopping criteria (usual criteria: a maximum of 6 increments of the validation error and a maximum of 1000 training epochs). Each MLP has 10 neurons for the hidden layer.

**Support Vector Regressor (SVR).** A support vector machine (SVM) is a supervised learning model that is mainly used for analyzing data for classification and regression analysis. Once a set of training data is given, it marks each point for classifying into categories using a non-probabilistic non-linear classifier based on the use of kernels, which allow mapping into higher-dimensional feature spaces to better discern the clustering of categories. When the SVM is used for fitting a response (i.e., regression) rather than classifying, it is called a support vector regressor (SVR). For the present study, the libSVM C++ library using the epsilon-SVR formulation with a Gaussian kernel (RBF) was used for solving the SVR problem. There are three configuration parameters: the epsilon value (default value 0.001), the algorithm Cost (optimized value) and the kernel’s Gamma (optimized value). The optimization of the parameters was achieved by searching the cross-validation generalized performance of the training data. This method uses a grid search within the maximum expectation range of the parameters (Cost and Gamma), yielding a surface where the minimum corresponds to the optimum.

Regarding the dataset used for both methods (MLP and SVR), it has been split as 80% of the data for the training stage and 20% for the validation stage. In addition, the models have been trained using k-fold techniques (with a k-fold equal to 5) to automatically optimize their parameters while avoiding overfitting during the training and differencing datasets according to populations (healthy, KTC and LASIK). Furthermore, the data have been normalized using the criterion of null average and the standard deviation equal to one.

**Quadratic Response Surface (QRS).** The response surface methodology seeks for the relationship between the input variables and the response variables in terms of the optimal response and using a dataset constructed following a sequence of designed experiments. In general, the method fits a multiple order surface (e.g., a second-order polynomial) to minimize the error with respect to the experimental data. In the present study, a multiple linear regression model including crossed and second-order terms was used for predicting the response \((D_1, D_2, k_1 \text{ and } k_2)\) as a linear function of the predictor variables. The model fitting used a stepwise regression (i.e., terms can be added or removed depending on their influence on the response) based on the Akaike information criterion (AIC). The AIC provides a measure of model quality by simulating...
Independent predictors were fit to the entire dataset and to individual populations to test their classification capabilities. Each predictor was structured as follows.

Let $j$ stand for a particular material parameter and $\chi_j$ be its predictor. Based on the ANOVA performed on the dataset, the most influential geometric parameters on the corneal displacement, $U$, are identified and denoted as $x$. Hence, each predictor $\chi_j$ was constructed as a function (inputs) of $x$, IOP, and the remaining material parameters of the model. Therefore, for parameter $D_1$, $\chi_{D_1} = \chi_{D_1}(x, IOP, D_2, k_1, k_2)$.

Once the models were trained, identification of the material parameters from the known patient data, i.e., $x$, IOP, and $U$, was performed iteratively using a fixed-point iteration algorithm. The search algorithm is detailed in Algorithm 1. In brief, $D_1$ is evaluated through $\chi_{D_1}$ using the material parameters from the previous iteration; $D_2$ will then be obtained through $\chi_{D_2}$ including the previously computed value for $D_1$, while $k_1$ and $k_2$ are kept from the previous iteration, and so on. The cost function controls the changes in the values of the material parameters between two consecutive iterations: if the change in the material properties between two consecutive iterations is less than a tolerance, the algorithm stops and the identified material parameters are reported.

**Algorithm 1.** Fixed-point iteration algorithm to determine material parameters from patient’s data (clinical biomarkers).

```matlab
% Initialize Control Values
TOL=1e-6; itemax=5000; k=1; error=1;

% Initialize Random Material Seed
mat^k=[D_1^k D_2^k k_1^k k_2^k];

WHILE AND(error>TOL,k<itemax)
    %Predict $D_1^{k+1}$
    D_1^{k+1}:=\chi_{D_1}(x,IOP, U, D_2^k, k_1^k, k_2^k);
    %Predict $D_2^{k+1}$
    D_2^{k+1}:=\chi_{D_2}(x,IOP, U, D_1^{k+1}, k_1^k, k_2^k);
    %Predict $k_1^{k+1}$
    k_1^{k+1}:=\chi_{k_1}(x,IOP, U, D_1^{k+1}, D_2^{k+1}, k_2^k);
    %Predict $k_2^{k+1}$
    k_2^{k+1}:=\chi_{k_2}(x,IOP, U, D_1^{k+1}, D_2^{k+1}, k_1^{k+1});
    k=k+1;
END
```

the situation where the model is tested on a different data set. After computing several different models, they can be compared using this criterion. According to Akaike’s theory, the most accurate model has the smallest AIC.
%Check Cost Function
\[ mat^{k+1} = (D_1^{k+1}, D_2^{k+1}, k_1^{k+1}, k_2^{k+1}); \]
\[ error = \sum |mat^{k+1} - mat^{k}|; \]

%Update Next Iteration
\[ k = k+1; \]
END

Neighborhood-Based Protocol (K-nn Search)

Due to the coupled effects that geometry, IOP, and material properties have on the corneal response (i.e., displacement), different combinations of parameters could exist that provide the same maximum displacement (i.e., less rigid corneas subjected to a large IOP could experience the same displacement to the air puff as a more rigid cornea subjected to a lower IOP), causing the response surface approach to be less effective, i.e., Algorithm 1 could identify different sets of material parameters according to the initial seed (local minima). The K-nn search approach searches the set of material parameters directly in the raw dataset without the need for an approximation function. This algorithm searches the \( n \) closest neighbors to the patient in the dataset and then interpolates the material model parameters in terms of the distance from the patient’s point to the neighbors. The distance is calculated as the Euclidean distance in the \((x, IOP, U)\) subspace of the dataset.

Validation

To validate the proposed methodology, 5 eyes (1 healthy eye and 4 keratoconus eyes) that were subjected to a non-contact tonometry test (CorVis ST, Oculus, Germany) were considered. For these eyes, the corneal topography, IOP and corneal displacement due to the air puff, \( U \), were available (see Table 4.1). These parameters were used to predict the patient’s material model parameters using the previously described predictors. With the predicted material model parameters and the topographical data of the cornea, an in silico non-contact tonometry test was simulated using the procedure proposed in Ariza-Gracia et al. 2015. The numerical corneal displacement, \( U_{\text{num}} \), was compared to the clinical displacement \( U \).

Computations and Statistical Analysis

Finite element simulations were conducted using the commercial finite element software Abaqus 6.11 (Dassault Systèmes Simulia Corp.). All the mathematical computations, algorithms and statistical analysis were developed using MATLAB.
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L. Eye | IOP [mmHg] | CCT [µm] | U [mm] | AL₁ [mm] | AL₂ [mm] | VA₁ [mm/ms] | VA₂ [mm/ms] | P. Dist. [mm] | R [mm]
---|---|---|---|---|---|---|---|---|---
ₗ₀ | R | 12 | 578 | 1.00 | 2.09 | 1.92 | 0.19 | -0.36 | 2.38 | 7.5
ₗtc₀ | R | 15 | 545 | 1.12 | 1.81 | 1.87 | 0.16 | -0.34 | 5.07 | 7.58
ₗtc₁ | L | 15 | 544 | 1.03 | 1.84 | 2.06 | 0.18 | -0.38 | 5.08 | 7.9
ₗtc₂ | R | 15 | 464 | 1.05 | 1.87 | 1.07 | 0.16 | -0.43 | 2.53 | 7.6
ₗtc₃ | L | 16 | 460 | 1.12 | 1.84 | 2.06 | 0.17 | -0.39 | 5.45 | 7.81

Table Legend and Units. L: identification tag (i.e., ‘ₗ’ for healthy eyes and ‘ₗtc’ for keratoconus eyes); Eye: ocular position; IOP [mmHg]: intraocular pressure; CCT [µm]: central corneal thickness; U [mm]: maximum deformation amplitude at the maximum concavity time; AL₁ [mm]: first applanation length; AL₂ [mm]: second applanation length; VA₁ [mm/ms]: velocity at the first applanation time; VA₂ [mm/ms]: velocity at the second applanation time; P. Dist. [mm]: peak distance; R [mm]: curvature at the maximum concavity time.

Table 4.1: Clinical Validation Data: CorVis Non-Contact Tonometry Test for Validation Patients (5 eyes: 1 healthy eye and 4 keratoconus eyes).

R2012 v.8.0. software and open source C++ libraries (libSVM C++). Data are reported as their mean and standard deviation (mean ± SD). Statistical significance was tested with the two-sample Kolmogorov-Smirnov test, where a two-sided p-value of less than 0.05 indicates significance. The performance of the predictors was measured in terms of the coefficient of correlation $R^2$ to measure the quality of the fitting, whereas the Akaike information criterion (AIC) was used to directly compare the quality of each model relative to each other.

4.3 Results

Monte Carlo Simulation

The Monte Carlo simulation computed 9,360 combinations. Due to technical limitations regarding the number of licenses, computations were performed on two conventional PCs with an 8-core processor and 8 GB RAM, requiring 128 days of computations on double thread. However, the methodology is implemented for a suitable parallel and massive computation on a computational cluster. The failure rate was under 3% of the computations, resulting in an effective dataset of 9,216 cases.

The simulations show that the proposed material model is adequate to reproduce both the inflation and the bending response of the cornea when subjected to an air puff for different levels of the IOP (see Fig.4.2.a). In particular, the range of parameters used for the Monte Carlo simulation is able to accommodate the experimental response to corneal inflation tests reported in the literature (see Fig. 4.2.b). Note that traditional model development for corneal mechanics has mainly considered inflation tests to identify the model parameters. However, when the response to an air puff is considered, we found that there are a number of combinations for which

36 Chang and Lin 2011
37 Sakamoto et al. 1986
Figure 4.2: Results of the Monte Carlo simulation. (a) Mechanical corneal response to both experiments: inflation and air puff. The physiological range for the inflation is limited by the inflation real curves reported in the literature [Whitford et al., 2015, Bryant and McDonnell, 1996] (see in black dashed lines and triangles), whereas the physiological range of the air-puff behavior must lie within the ‘searching objective frame’ (i.e., the reported experimental displacement to CorVis [Lanza et al., 2016]). As shown in the ‘upper right area’, a physiological inflation behavior could not represent a physiological air-puff mechanical response, and thus, aiming out of the searching frame (see yellow vs. red lines in the figure); (b) First Monte Carlo analysis for pre-screening the range of the material parameters within the physiological inflation range reported. From all the simulations, the extreme ones were chosen for constraining the search space of the second Monte Carlo analysis. The range of the material parameters is shown in the bottom of the panel; (c) Second Monte Carlo analysis for establishing the range of the corneal mechanical response to an air-puff test. All the mechanical responses (incremental displacement due to the incremental pressure) related to the material range variation are depicted in a lighter color in the figures. Darker zones belong to those combinations of material parameters that numerically behaved as physiological with respect to the maximum deformation amplitude reported in the CorVis diagnosis. (c.1) Results of the Monte Carlo simulation for those eyes classified as healthy in the clinic (i.e., those whose topography and IOP were diagnosed as healthy by an optometrist). Dark red curves belong to the simulations that cast a numerical displacement that is contained within the experimental range \( U_{Healthy}[mm] \in (0.8, 1.1) \); (c.2) Results of the Monte Carlo simulation for those eyes classified as keratoconic in the clinic. Dark blue curves belong to the simulations that cast a numerical displacement that is contained within the experimental range \( U_{KTC}[mm] \in (0.95, 1.25) \); (c.3) Results of the Monte Carlo simulation for those eyes that were subjected to a LASIK surgery in the clinic. Dark green curves belong to the simulations that cast a numerical displacement that is contained within the experimental range \( U_{LASIK}[mm] \in (0.9, 1.15) \).
the inflation response is within the experimental range but the corneal displacement due to the air puff is not. An example of this situation is given by the red and blue lines in Fig. 4.2.a. In both cases, the response to the inflation test is identical, but the response to the air-puff is not physiological for the red line. Therefore, from the total number of samples in the Monte Carlo simulation, only those samples that reconcile the response to an inflation and to an air puff test to be within the experimental ranges were considered.\textsuperscript{38} After including this exclusion criterion, only 29\% (1127 of 3855) of the healthy cases, 30.5\% (1327 of 4344) of the KTC cases, and 21.5\% (219 of 1017) of the LASIK cases were included in the training dataset. The bright areas in Fig. 4.2.c(1–3) (healthy: red; KTC: blue; LASIK: green) show the response to the air puff for the admitted samples.

The empirical distribution of the material parameters related to the matrix ($D_1$ and $D_2$) did not follow a uniform distribution, whereas those related to the fibers ($k_1$ and $k_2$) were found to be uniformly distributed (see 4.6 in 4.5). A Kolmogorov-Smirnov test shows non-significant differences between the material parameters of the healthy-LASIK and the KTC-LASIK populations (see in Table 4.2). In contrast, significant differences were found for $D_1$ and $D_2$ between the healthy-KTC populations.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>$D_1$</th>
<th>$D_2$</th>
<th>$k_1$</th>
<th>$k_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy–KTC</td>
<td>$h$</td>
<td>$p$-value</td>
<td>$h$</td>
<td>$p$-value</td>
</tr>
<tr>
<td>Healthy–LASIK</td>
<td>0</td>
<td>0.869</td>
<td>0</td>
<td>0.779</td>
</tr>
<tr>
<td>KTC–LASIK</td>
<td>0</td>
<td>0.098</td>
<td>0</td>
<td>0.161</td>
</tr>
</tbody>
</table>

*Table Legend.* $h$: indicates the result of the hypothesis test (i.e., $h=1$ rejects the null hypothesis that both populations come from the same continuous probability distribution); $p$-value: asymptotic $p$-value of the test (i.e., $p$-value $<0.05$ means that the null hypothesis can be rejected at a 5\% significance level).

When the cornea is under the action of the IOP (i.e., its physiological stress state), the cornea is under a pure traction membrane stress state where the full cornea works in tension (i.e., both extracellular matrix and both families of collagen fibers), and therefore, no bending effects exist. However, during an air puff, the cornea experiences bending. Whereas the anterior surface goes from a traction state of stress to a compression state of stress, the posterior surface works in tension. Hence, in the anterior corneal stroma, the collagen fibers are not contributing to load bearing since they do not support buckling and the stiffness of the cornea mainly relies on the extracellular matrix. At the same time, the collagen fibers on the posterior stroma suffer from a higher elongation, resulting in an overall non-physiological state of stress. In this regard, due to the action of the IOP, no significant differences in the maximum principal stress and in the maximum principal

\textsuperscript{38} Lanza et al. 2016, Huseynova et al. 2014, Hassan et al. 2014
stretch were observed between the different populations for both the anterior and posterior corneal surfaces. In contrast, when the maximum principal stress and stretch are compared at the instant of maximum corneal displacement, significant statistical differences between all populations were found at the posterior surface (see Table 4.3). However, at the anterior surface, significant differences were found only for the maximum principal stretch, whereas for the maximum principal stress, differences were found only between the healthy and KTC populations (see Table 4.3).

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Anterior Stretch</th>
<th>Anterior Stress</th>
<th>Posterior Stretch</th>
<th>Posterior Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>h</td>
<td>p-value</td>
<td>h</td>
<td>p-value</td>
</tr>
<tr>
<td>Healthy–KTC</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Healthy–LASIK</td>
<td>1</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.073</td>
</tr>
<tr>
<td>KTC–LASIK</td>
<td>1</td>
<td>&lt;0.001</td>
<td>0</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Table Legend. h: indicates the result of the hypothesis test (i.e., h=1 rejects the null hypothesis that both populations come from the same continuous probability distribution); p-value: asymptotic p-value of the test (i.e., p-value < 0.05 means that the null hypothesis can be rejected at a 5% significance level).

Sensitivity Analysis

The sensitivity analysis and ANOVA conducted on the dataset (with the admitted samples only) demonstrate the predominant role of the material parameters on $U_{num}$ (see Fig.4.3.a). For the entire population, ANOVA revealed that the most influential parameters are the material parameters ($D_1$ and $D_2$), followed by the IOP and the central corneal thickness (CCT). When the populations are considered separately (Fig.4.3.b and Fig.4.3.c, respectively), the general trends are kept for the healthy and LASIK populations. However, for the KTC population, the IOP appears to play a more important role than the material itself. In addition, the superior-inferior curvature slightly influences the numerical response for the KTC population. The results demonstrate the significant importance of the IOP on $U$ for those cases in which the corneal thickness is lower relative to the healthy case (i.e., KTC and LASIK).

In general, the sensitivity analysis showed that the most influential parameters on the displacement response ($U_{num}$) were the material parameters ($D_1$, $D_2$ and $k_2$), the intraocular pressure (IOP), and the central corneal thickness (CCT) in all populations. An exception is found for the superior-inferior curvature ($R_V$) for the KTC population. However, the most remarkable result is the negligible impact of the material parameter $k_1$ on the numerical response. Although $k_1$ cannot be removed from the simulations since it is a material parameter of the strain energy function
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Figure 4.3: Pareto chart representing the variables responsible for 95% of the mechanical response (displacement). (a) Impact of the main variables on the mechanical response taking the entire dataset into account; (b) Impact of the main variables on the mechanical response taking the healthy cases of the dataset into account; (c) Impact of the main variables on the mechanical response taking the KTC cases of the dataset into account; (d) Impact of the main variables on the mechanical response taking the LASIK cases of the dataset into account. Legend: intraocular pressure (IOP), central corneal thickness (CCT), superior-inferior curvature of the eye (\(R_v\)), material parameters (\(D_1, D_2, k_2\)) and interaction between material parameter \(D_1\) and the intraocular pressure (\(D_1 : IOP\)).

(4.1), the result from the sensitivity analysis suggests that setting its value to its average (i.e., \(k_1 = 19\) [kPa]) appears to be a reasonable choice in terms of developing the material predictors. Henceforth, the parameter \(k_1\) is treated as a constant value, thereby avoiding the need to adjust or train a specific model for it, with a consequent reduction in computational cost.

Response surface predictor models (MLP, SVR and QRS)

According to the results from the sensitivity analysis, the predictive models were constructed considering \(D_1, D_2, k_2, IOP, CCT,\) and \(U_{num}\), following the methodology described in Materials and Methods. Table 4.4 presents the main results from the fitting for the three models under consideration.

All response surface methods performed similarly, although the MLP model showed a slightly better performance (see the \(R^2\) value in Table 4.4). All models (\(D_1, D_2,\) and \(k_2\)) presented a good coefficient of determination (\(R^2\)) and a relatively low dispersion of the residuals (i.e., predicted response minus real response) with their mean around zero, with the exception of \(k_2\), which presented a higher dispersion. This result was somewhat expected since \(D_1\) and \(D_2\) were the material parameters to which the corneal displacement was more sensitive. In general, the best fitting always corresponded to the healthy population, whereas the worst performance was always found for the LASIK population. These results could be thought to be related with the disruption of the collagen fibers due to the corneal flap generated
Table 4.4: Accuracy for the four predictors (MLP: multiple layer perceptron; SVR: support vector regressor; SR: surface response) for the different populations (healthy, KTC and LASIK)

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>KTC</th>
<th>LASIK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLP</td>
<td>SVR</td>
<td>QRS</td>
</tr>
<tr>
<td>D1</td>
<td>R²</td>
<td>-1769</td>
<td>-1661</td>
</tr>
<tr>
<td></td>
<td>µres</td>
<td>-0.002</td>
<td>-0.005</td>
</tr>
<tr>
<td></td>
<td>σres</td>
<td>0.028</td>
<td>0.032</td>
</tr>
<tr>
<td>D2</td>
<td>R²</td>
<td>0.962</td>
<td>0.954</td>
</tr>
<tr>
<td></td>
<td>µres</td>
<td>-0.295</td>
<td>-0.622</td>
</tr>
<tr>
<td></td>
<td>σres</td>
<td>5.408</td>
<td>5.912</td>
</tr>
<tr>
<td>k²</td>
<td>R²</td>
<td>0.857</td>
<td>0.822</td>
</tr>
<tr>
<td></td>
<td>σres</td>
<td>148.2</td>
<td>164.0</td>
</tr>
</tbody>
</table>

Table Legend: R²: coefficient of determination; AIC: Akaike information criterion for the final adjusted model; µres: average of the residuals of the predicted response with respect to the expected response; σres: standard deviation of the residuals of the predicted response with respect to the expected response.
during the surgery and its consequent loss of stiffness. However, since our models are phenomenological and not structural, the dispersion is hypothesized to be mainly associated with the abrupt change of the corneal curvature of the anterior surface due to the resulting flattened area induced by the surgery and the dispersion on the central corneal thickness. As mentioned in the Materials and Methods section, in addition to individual predictors of the material parameters for each of the populations, a predictor was fit for each material parameter but considering the entire dataset. No significant differences in the results were obtained when compared with the predictors constructed for individual populations (results not shown). Therefore, in the following, only results corresponding to individual populations will be shown.

Regarding the Akaike information criterion, it remains almost constant between the methods (MLP, SVR and QSR) for the same parameter \( (D_1, D_2 \text{ and } k_2) \), indicating that all models obtained similar quality on the adjustment. The residual analysis indicates that the best predictions (i.e., mean close to 0) always belong to the \( D_1 \) independently of the method and the population. In contrast, the worst predictions were always associated with \( k_2 \) independently of the method and the population. However, it is remarkable that the healthy population showed the best accuracy with respect to the rest of the populations, whereas the KTC population showed the worst accuracy. This finding could be explained by the inherent geometrical variability of the keratoconus. For this pathology, the location of the disease is not repeatable among patients, leading to a very heterogeneous distribution of geometrical features among patients. Conversely, the geometrical features of healthy eyes are more repeatable. Furthermore, the better accuracy of the \( D_1 \) and the \( D_2 \) parameters are directly supported by their importance on the corneal response of the model (see Fig.4.3).

**Neighborhood-Based Protocol (K-nn Search)**

The K-nn search method does not require the fitting of a particular mathematical function to predict the material parameters in terms of the corneal patient's geometric data and the mechanical response to the air puff since it simply searches for the closest point in the database to the patient's data (IOP, CCT and \( U \)). However, this method helps to demonstrate the inherent coupling that exists between CCT, IOP and \( U \) that has been demonstrated in previous studies.\(^{39}\)

Figure 4.4a shows that for a given value of the IOP, different combinations of the material properties and corneal thickness lead to the same corneal displacement, \( U \) (see red dots in Fig. 4.4a). Similarly, for a given corneal thickness, different combinations of material parameters and IOP provide the same corneal displacement as an air puff (see Fig.4.4.b). This result shows that different combinations...
Figure 4.4: Coupled Effect of the Corneal Response (Patient h0, Table 4.1). All the healthy cases of the dataset are represented as blue dots in the figures. The biomarkers selected for determining the mechanical properties of the eye are shown to outline the coupling between different parameters: different combinations of thickness, material and intraocular pressure could lead to the same displacement. (a) Displacement ($U$) versus thickness (CCT) considering the intraocular pressure to be constant (IOP=12 mmHg). In red dots, all the feasible combinations of CCT that lead to the same displacement (1 mm) when the material properties and the pressure are fixed; (b) Displacement ($U$) versus IOP (IOP) considering the thickness to be constant (CCT=578 microns). In red dots, all the feasible combinations of IOP that lead to the same displacement (1 mm) when the material properties and the CCT are fixed; (c) Intraocular pressure (IOP) versus thickness (CCT) considering the displacement to be constant ($U=1.00$ mm). All tuples of IOP and CCT that can lead to the same displacement (1 mm). The dispersion of the parameters is only influenced by the tissue stiffness, i.e., the lowest pressures and thickness can only behave as the highest pressures and thickness if the material properties are stiffer. In this way, although different corneas could have a similar average tissue stiffness, an increase in IOP or CCT could lead to a less compliant mechanical response.
of material parameters, IOP and CCT can lead to the same corneal displacement, \( U \), thus making it impossible to quantify each contribution separately. However, when the patient-specific information (IOP, CCT, and \( U \)) is used as an input to the dataset (red triangle in Fig.4.4.c), it is possible to define a neighborhood of feasible points around the patient's data (blue diamonds in Fig.4.4.c) from which the material parameters can be estimated. This method is the most straightforward in terms of searching and implementation, as well as the one providing the best prediction (see next section). However, it is also the most expensive method in terms of computations since the accuracy of the method is highly affected by the resolution of the grid used for the dataset (number of samples present in the dataset).

<table>
<thead>
<tr>
<th>L.</th>
<th>Meth.</th>
<th>Input</th>
<th>Output ( D_1 )</th>
<th>( D_2 )</th>
<th>( k_1 )</th>
<th>( k_2 )</th>
<th>Validation ( U_{num} )</th>
<th>( \epsilon(%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( h_0 )</td>
<td>K-nn</td>
<td>IOP=12 mmHg</td>
<td>0.277</td>
<td>120.6</td>
<td>20.8</td>
<td>516.9</td>
<td>1.007</td>
<td>0.726</td>
</tr>
<tr>
<td></td>
<td>QRS</td>
<td>CCT=578 ( \mu )m</td>
<td>0.193</td>
<td>138.3</td>
<td>19.0</td>
<td>545.6</td>
<td>1.013</td>
<td>1.251</td>
</tr>
<tr>
<td></td>
<td>MLP</td>
<td>U=1.00 mm</td>
<td>0.446</td>
<td>85.7</td>
<td>19.0</td>
<td>843.1</td>
<td>1.022</td>
<td>2.158</td>
</tr>
<tr>
<td></td>
<td>SVR</td>
<td></td>
<td>0.292</td>
<td>122.8</td>
<td>19.0</td>
<td>191.5</td>
<td>1.006</td>
<td>0.573</td>
</tr>
<tr>
<td>( ktc_0 )</td>
<td>K-nn</td>
<td>IOP=15 mmHg</td>
<td>0.267</td>
<td>103.5</td>
<td>17.9</td>
<td>525.3</td>
<td>1.153</td>
<td>2.968</td>
</tr>
<tr>
<td></td>
<td>QRS</td>
<td>CCT=545 ( \mu )m</td>
<td>0.289</td>
<td>97.9</td>
<td>19.0</td>
<td>455.5</td>
<td>1.175</td>
<td>4.917</td>
</tr>
<tr>
<td></td>
<td>MLP</td>
<td>U=1.12 mm</td>
<td>0.379</td>
<td>80.6</td>
<td>19.0</td>
<td>644.6</td>
<td>1.174</td>
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<td></td>
<td>0.368</td>
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<td>687.4</td>
<td>1.171</td>
<td>4.503</td>
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<td>( ktc_1 )</td>
<td>K-nn</td>
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<td>0.330</td>
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<tr>
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<td>0.320</td>
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<td>458.4</td>
<td>1.042</td>
<td>1.150</td>
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<td>19.0</td>
<td>443.0</td>
<td>1.072</td>
<td>4.099</td>
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<td>0.229</td>
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<td>( ktc_2 )</td>
<td>K-nn</td>
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<td>0.385</td>
<td>126.7</td>
<td>20.8</td>
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<tr>
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<td>QRS</td>
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<td>K-nn</td>
<td>IOP=16 mmHg</td>
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<tr>
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<td>1.198</td>
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<td>486.6</td>
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</table>

Table Legend: (\( D_1 \) [kPa] | \( D_2 \) [-] | \( k_1 \) [kPa] | \( k_2 \) [-]): Parameters of the Demiray + G-H-O energy strain function; \( U_{num} \) [mm]: maximum deformation amplitude provided by the numerical simulation of the non-contact tonometer; \( \epsilon(\%) = |U_{num} - U| / U \times 100 \): percentage difference between numerical and clinical displacement.

**Examples with clinical data**

Table 4.5 shows the material model parameter predictions for the 5 patients described in Table 4.1. All the material model parameters obtained with the different
predictors were used to simulate a non-contact tonometry test using the patient-specific data available for each case, i.e., topography of the cornea and IOP. For most cases, the predicted displacements ($U_{\text{num}}$) were in close proximity to the measured displacement ($U$), with the largest error difference, $\epsilon(\%)$, being 13% for the KTC eye (patient ktc2) and the QRS method. In addition, although local minima exist and we are aware of them, material predictions associated with local minima also lead to a predicted corneal displacement close to the actual measurements (results not shown). For patient ktc2, for which the material predictions led to the worst corneal displacement predictions, it was found that the closest neighbor to the patient's data was located at a distance that was an order of magnitude larger than for the other patients. This result indicates the need for a larger number of samples in the dataset, i.e., a more dense sampling of the parameter space. However, note that as the number of patients in the database increases, the prediction capabilities of all models will also generally increase. Further information regarding the performance of each method can be found in 4.5. Regarding the time required to search a set of material parameters ($t_{\text{exec}}$, Table 4.6), the fastest method is the K–nn search since it does not require any iterative procedure to find the material properties. In addition, depending on the initial material seed, the iterative procedure may find different minima and take longer execution times. For these reasons, the implementation of the algorithm includes a multiple seed strategy to identify the material parameters with the least possible error.

### 4.4 Discussion

A series of mathematical models have been proposed to predict the mechanical properties of corneal tissue from patient-specific data obtained using a non-contact tonometry test. The proposed methodology is based on in silico simulations of the non-contact tonometry tests using patient-specific corneal geometry data. The methodology is amenable for implementation on commercial devices for clinical applications, and it provides acceptable execution times and accuracy.

The computational simulation has different assumptions of the material and the modeling that cannot be neglected. First, we used a phenomenological and macroscopic material model for the cornea that allows to reproduce, within the experimentally reported range, the corneal response to both inflation to increase values of IOP and the corneal displacement induced by a non-contact tonometry test. Regarding the material model, there are some hypotheses that must be addressed, such as the absence of viscoelasticity or the use of a generic orthogonal pattern of fibers following that proposed by Meek et al. (2009). With respect to the viscoelastic properties of the cornea, the loading of the tissue is fast enough to consider that viscoelastic effects do not play a major role in the corneal response.

---

40 Ariza-Gracia et al. 2016b

41 Meek and Boote 2009

42 Simo 1987
This assumption has been widely accepted in previous publications (see several publications by Elsheikh, Pandolfi, Lanchares or Studer), and recently, Simonini et al. (2016) have reported a study on the dynamics of the cornea when subjected to an air puff that suggests the great importance of the elastic contribution of the stroma during the loading phase of the air jet but the minor contribution of the inertia and viscoelasticity. However, if the recovery of the cornea during the unloading phase would be addressed, the inclusion of inertia and viscoelasticity would be essential. Concerning the pattern of collagen fibers is not patient specific since it is not yet easily accessible. Although Winkler et al. and others authors have reported a more precise micro-structural distribution of the fibers using SHG optical microscopy, the inclusion of the patient-specific micro-structural information of the cornea would not be useful but would rather increase the computational costs and introduce a new bias since this information was not accessible for our patients. Nevertheless, the proposed methodology does not prevent the use of more complex material models that incorporate information of the micro-structure of the cornea, viscoelasticity or inertia. Second, the boundary condition simulating the air-jet impact has been assumed to be a constant pressure applied over the cornea. Although a CFD analysis has been applied over a generic cornea to compute the pressure pattern, a more precise simulation would require a fluid structure simulation since the corneal geometry and the deformation of the cornea over time may have an important impact on the pressure transferred during the air puff.

Despite its considerable computational cost, the Monte Carlo simulation has proven to be a powerful tool for use in real-time estimation of the corneal mechanical properties from a non-contact tonometry test in the clinic. In addition, the mathematical tools (MLP, SVR and QRS) have shown good performance in predicting the corneal material parameters, but the inherent coupling between the IOP, the CCT, and the corneal mechanical properties affecting the corneal response introduces an unavoidable dispersion in the data that reduces the performance of these methods. In this regard, the K–nn search has proven to be the most reliable method. Since it restricts the search to the neighborhood of the patient, the method is not prone to finding local minima, and it exhibits the best performance in terms of execution time. Furthermore, the material model parameters predicted by the K-nn search method lead to the most accurate predictions of the corneal displacement with respect to the clinical value (i.e., less than 3% difference with respect to the clinical results). Although the main drawback is the considerable computational cost involved in generating the dataset because it needs a fine resolution on the data grid for good accuracy, it is still more suitable than other optimization methods, such as the IFEM, due to its real-time response (i.e., no finite element computation is required for the diagnosis, but the patient can subsequently be used for updating the dataset).
No significant differences have been found between populations, in general, in terms of the material parameters. In this regard, only the healthy and KTC populations showed significant differences in terms of the $D_1$ and $D_2$ parameters but not in terms of $k_1$ and $k_2$. Therefore, these results indicate that considering differences in the material parameters of the cornea may not be sufficient to classify healthy and keratoconus eyes using a single air-puff test, pointing to the necessity of having more than a single test for properly characterizing the properties of the eye. However, until now, there has been no additional \textit{in vivo} test that complements the air-puff diagnosis, and the results should be assessed additionally by, for example, \textit{ex vivo} inflation tests, as we used for constraining the search of material properties with both physiological behaviors (i.e., inflation and air puff). Moreover, our results suggest that variations in corneal thickness may be a more reliable monitoring variable in terms of classifying the healthy population from the KTC population. In addition, based on the finite element simulations, the maximum principal stretch in the anterior and posterior surfaces of the cornea obtained at the instant of maximum corneal deformation may be used as a discriminant to classify different groups (healthy, KTC and LASIK).

One final limitation regarding the clinical biomarkers used for the prediction must be addressed. For simplicity, only 3 clinical biomarkers have been used for predicting the material properties of the cornea: pressure (i.e., the IOP), geometry (i.e., CCT) and displacement (i.e., the maximum deformation amplitude of the CorVis test). Since our models are mainly phenomenological, macroscopic and are not taking the inertia, viscoelasticity and micro-structural features of the cornea into account, the dynamic parameters provided by the CorVis diagnosis test cannot be trustworthily used. Moreover, ANOVA and the Pareto analysis showed that for the models used in the present study, the most influential parameters were the selected ones. However, there are no problems for easily introducing other corneal parameters in the predictive model, provided that they can be accurately measured in both the experimental and the numerical results. Although only these 3 biomarkers have been used, the methodology has been tested with actual unknown patient data that did not form a part of the dataset. The predicted material parameters, along with the patient’s corneal geometry and IOP, were used to simulate a non-contact tonometry test to predict the corneal displacement. The numerical results resulted in errors of less than 10% in most cases, with the K-nn search methodology outperforming the response surface-based methods, achieving errors of less than 3%.

The important aspect of the present study is that the proposed methodology, independently of the complexity of the numerical simulations, is amenable for real-time diagnosis and implementation in commercial devices. Importantly, it allows easily introducing additional elements (e.g., viscoelasticity, microstructure, dynamics, and so forth) that could enhance the performance and accuracy of the results without
modifying the underlying methodology. Eventually, the computational framework will incorporate actual clinical data (corneal topographies, IOP and corneal apical displacement from a non-contact tonometry test) to predict the mechanical properties of the cornea. These results could be used for surgical planning or to monitor the evolution of a given patient by looking at changes in the mechanical properties with time.

4.5 Additional Results

This appendix contains the extended non-essential results that are needed to understand the complete scope of the outcomes. The extensions are related to the following:

- **Sensitivity analysis**: The response surface ($U = f(\text{geometry, pressure, material})$) used for analyzing the impact of the different variables (geometry, pressure and material) to the numerical variable under analysis in the FE computation (displacement) is depicted in Fig.4.5.

- **Statistical distribution of the mechanical properties of the cornea for the Monte Carlo simulation**: All the Monte Carlo combinations of material that fulfill both physiological responses (inflation and air puff) are presented in Fig.4.6 (green histogram). Whereas the parameters related to the fibers are uniformly distributed ($k_1$ and $k_2$), the matrix parameters ($D_1$ and $D_2$) stack around 0.4–0.45 [kPa] and [130–140].

- **Accuracy of the prediction after the training phase for the SVR and MLP**: The accuracy of the predictions of both methods after the training phase is depicted in Fig.4.7. Support vector regressor does not present a blue shaded zone since only one SVR is used. Conversely, the MLP uses 7 different assemblies and subsequently computes the average. Therefore, the confidence intervals (blue shaded zones) can be established.

- **Goodness of the fits for the SVR, MLP and QRS models**: The correlation plot of the predicted property versus the actual value in the dataset is depicted in Fig.4.8. The material properties $D_1$ and $D_2$ show the best model fitting, whereas $k_2$ shows a higher dispersion ($k_1$ is not shown since it was discarded after the sensitivity analysis).

- **Additional performance of the methodology**: The results of supplementary performance variables (execution time, distance of the nearest neighbor and initial tangent modulus) are depicted in Table 4.6.
Figure 4.5: Slice plots of the quadratic response surface for each population (healthy—red, KTC—blue, LASIK—green). The slice plots show the individual contribution of the different model parameters on the numerical displacement. The higher the slope, the higher the contribution (shaded zones represent the standard deviation of the parameter, whereas solid lines represent the mean response). (a) Impact of the model parameters on the numerical displacement of the healthy population; (b) Impact of the model parameters on the numerical displacement of the KTC population; (c) Impact of the model parameters on the numerical displacement of the LASIK population.
Methods for Characterising Patient-Specific Corneal Biomechanics

Figure 4.6: Statistical distribution of the mechanical properties of the cornea for the Monte Carlo simulation. The empirical distribution (green histogram) due to all the combinations of material parameters that fulfill both physiological behaviors (inflation and air puff) shows that the fiber’s parameters are uniformly distributed.

Table 4.6: Performance of the Prediction of the Patient-Specific Material Properties for the Clinical Patients (Table 4.1) Applying the Prediction Models (K-nn Search: Neighbor-based Prediction Model; QRS: Quadratic Response Surface Model; MLP: Multiple Layer Perceptron; SVR: Support Vector Regressor)

<table>
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<tr>
<th>L.</th>
<th>Meth.</th>
<th>( t_{\text{exec}} ) [s]</th>
<th>Dist. [-]</th>
<th>E [kPa]</th>
<th>E [%]</th>
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<td>( h_0 )</td>
<td>K-nn</td>
<td>0.060 ± 0.023</td>
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<td>4.091 ± 0.269</td>
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<td>306.076</td>
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Table Legend: \( t_{\text{exec}} \) [s]: execution time for prediction; Dist. [-]: minimum distance of the neighborhood (only for K-nn search); \( E = 6 \cdot D_1 D_2 + 4 \cdot k_1 \) [kPa]: Equivalent initial tangent modulus (\( \lambda = 1 \)); \( E(\%) = 100 \cdot (1 - E_j / E_{K-nn}) \): initial slope difference between the equivalent initial tangent modulus of the \( j \) method \( (E_j) \), where \( j \) are QRS, MLP, and SVR, with respect to the equivalent initial tangent modulus of the K-nn search method \( (E_{K-nn}) \).
Figure 4.7: MLP (right panel) and SVR (left panel) predictions for validating the training phase (only healthy response is shown). a.(1–3): $D_1$, $D_2$ and $k_2$ predictions depending on the patient case for the MLP method. Blue intervals correspond to the confidence interval (95% light blue and 99% dark blue) of the prediction since the method is composed of an ensemble of 7 independent MLPs and the response is the average of each independent MLP; b.(1–3): $D_1$, $D_2$ and $k_2$ predictions depending on the patient case for the SVR method. $k_1$ predictor is not computed since it was discarded after the sensitivity analysis.
Figure 4.8: Correlation plot of the predicted parameter (y-axis) vs expected parameter (x-axis) for the healthy group. a.(1–3): QRS; b.(1–3): MLP; c.(1–3): SVR. $D_1$ and $D_2$ show a good prediction of the values, whereas $k_2$ presents a higher dispersion. $k_1$ predictor is not computed since it was discarded after the sensitivity analysis.
5

Numerical-Experimental Protocol to Determine Corneal Properties

I have a number of alternatives, and each one gives me something different.

Glenn Hoddle

This chapter details the development of an alternative numerical-experimental protocol to determine the mechanical properties of the corneal tissue. Besides, the prediction of a refractive surgery is carried out to validate the methodology.

Chapter Contents

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5.1 Introduction

In visual healthcare, an increasing number of efforts are being made toward proper corneal characterization to assess refractive surgeries,\(^2\) to study the effect of intracorneal segment rings (ICRS) in keratoconus stabilization,\(^3\) to plan better surgical interventions, and to qualitatively predict the evolution of a pathology.\(^4\) Commercial devices aim at discerning the quality of corneal tissue by applying external pressure to the cornea (i.e., tonometers). Contact tonometers (e.g., Goldmann applanation tonometry) determine the intraocular pressure (IOP) of the eye. Non-contact tonometers, or air-puff tonometers (e.g., CorVis ST and Oculus), aim at determining the IOP and the quality of the corneal tissue based on the corneal deformation.\(^5\) There are important differences between them. Contact tonometers use a small plastic cylinder to indent the cornea (i.e., a displacement-driven contact test), whereas non-contact tonometers use an air jet to induce the motion of the cornea (i.e., a force-driven non-contact test). Although useful, non-contact tonometers have several associated uncertainties, such as the exact area affected by the air jet, the distance and alignment of the patient with the device, and the intrinsic geometry of the patient’s cornea. Thus, displacement-driven contact tests are more reliable since they accurately control the application and positioning of the force during the test, reducing the bias introduced in the experiments. Finally, there is generally a difference in the type of loading applied by tonometers to induce non-physiological stresses on the corneal tissue.\(^6\)

In contrast to the natural membrane-like state of stress of the cornea, tonometers bend the corneal tissue. When the eyeball is physiologically loaded (i.e., biaxial tension due to the IOP; see white point in Figure 5.1.a), the embedded collagen fibers are under tension and contribute to load bearing. However, during a tonometry test, the stress state of the anterior and posterior stroma changes. As the cornea bends, the stress state of the anterior stroma changes to compression, while the posterior stroma is much more tensioned (see the square and inverted triangle close to the solid black dot in Figure 5.1.a).

The cornea is mainly composed of water and collagen fibers embedded in an extracellular matrix. Therefore, associated material models estimate a nearly incompressible anisotropic hyperelastic behavior in which the extracellular matrix and the fibers are generally uncoupled.\(^7\) These models represent the corneal behavior observed in experiments.\(^8\) Currently, different experimental protocols are used to characterize the corneal tissue: uniaxial tensile tests,\(^9\) vibration tests,\(^10\) and inflation tests.\(^11\) Furthermore, Kok et al. 2014 noted that calibrating a corneal material model using a single inflation test is an ill-posed problem. In other words, different sets of properties can be obtained when calibrating the corneal tissue parameters within the same experiment.

\(^2\) Studer et al. 2013
\(^3\) Kymionis 2015
\(^4\) Romero-Jiménez et al. 2010, Summers and Harper 2015
\(^5\) Piñero and Alcón 2014
\(^6\) Ariza-Gracia et al. 2015, 2016b
\(^7\) Pandolfi and Holzapfel 2008, Elsheikh et al. 2013
\(^8\) Bryant and McDonnell 1996, Elsheikh et al. 2015
\(^9\) Pandolfi and Boschetti 2015
\(^10\) Kling et al. 2014a
\(^11\) Elsheikh et al. 2015
To overcome this limitation, a numerical-experimental protocol is proposed to characterize the corneal tissue parameters. The novelty of this protocol relies on using both inflation and indentation experiments to identify the optimal set of material parameters. First, the experimental protocol characterizes the corneal geometry and the mechanical response to both tests. Second, a numerical optimization based on an inverse finite element methodology (iFEM) identifies the set of material properties that satisfies both mechanical responses. To validate the model, four New Zealand rabbits were subjected to astigmatic keratotomy (AK) surgery. In normal clinical practice, AK surgery is used to modify the curvature of the cornea in order to reduce astigmatism, modifying a more elliptical cornea to a more spherical cornea. However, as New Zealand rabbits have an almost spherical cornea with circumferential collagen fibers, in our experiments, the surgery had the opposite effect of increasing astigmatism. To control the corneal optics, the pre- and post-surgical topographies of the anterior corneal surface were acquired using a MODI corneal topographer (Construzione Strumenti Oftalmici, CSO, Florence, Italy). An in-house optical software was developed to obtain the refractive power and the wavefront aberration of the optical system. Finally, before the refractive surgery, the optical outcomes were predicted using the optimal set of material parameters on average and patient-specific geometries.

5.2 Material and Methods

To ensure a correct sequence, the Material and Methods section is organized according to the research timeline. First, the Experimental Protocol section collects all the information regarding the experimental characterization: the selection of animals and ethics guidelines, the geometrical characterization and the measurements of intraocular pressure, the mechanical characterization of the cornea via inflation and experimentation experiments, and the in vivo ocular refractive surgery performed to validate the model. Second, the Numerical Protocol section collects all the information regarding the simulations used to perform the material characterization via an inverse finite element methodology: the constitutive equation, the finite element modeling, and the algorithm developed to reproduce the experimental protocol in silico. Finally, the material parameters obtained using the inverse characterization are utilized to numerically predict the optical outcomes of the real refractive surgery.
Experimental Protocol

Animals

Adult male New Zealand white rabbits (weighing between 1.8 and 2.2 kg) obtained from the Animal Experimentation Service of the Research Support Services of the University of Zaragoza were used. The animals were watered and fed with a standard chow diet ad libitum (Finished feed n. 511; Food Corporation Guissona S.A., Lleida, Spain) and housed individually. All animals were healthy and free of clinically observable ocular disease and showed no abnormalities in an ophthalmic examination consisting of the Schirmer tear test (Schirmer Tear Test Strips paper®; Madhu Instruments, New Delhi, India), slit-lamp biomicroscopy (Topcon SL-8Z®; Topcon Corp., Barcelona, Spain), fluorescein staining (Fluorescein paper®; HaagStreit Internacional, Liebefeld-Bern, Switzerland) and direct ophthalmoscopy (Heine beta 200®; Heine Optotechnik GmbH & Co., Herrsching, Germany).

This research was conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. All procedures were carried out under Project Licence 15/13 approved by the in-house Ethics Committee for Animal Experiments of the University of Zaragoza. The care and use of animals were performed according to the Spanish Policy for Animal Protection RD 53/2013, which meets the European Union Directive 2010/63 on the protection of animals used for experimental and other scientific purposes.

Geometrical Characterization of the Cornea

Computational models require the geometry of the cornea and its physiological state. The most important parameters are the corneal curvature (CC), the corneal thickness (CT) and the IOP. The CC was measured using a corneal topographer (MODI 2®, CSO, Scandicci, Italy). A map of 17 symmetric points of the CT was obtained. The value of each point is the average of 10 values recorded with a solid contact ultrasonic probe (DGH 500 PachetteTM, DGH Technologies Inc., Exton, USA). The IOP is the average of 3 measurements (95% confidence) using an applanation tonometer (TonoPen XL®, Medtronic Inc., Jacksonville, USA). Measurements were performed by the same experienced researcher (Á.O.) in both eyes of 6 animals. To avoid circadian variations in the IOP and the CT, all measures were performed within a defined time window (11:00–13:00).

Mechanical Characterization: Inflation and Indentation tests

For the ex vivo mechanical characterization, four rabbits were humanely euthanized with an overdose of intravenous sodium pentobarbital (150 mg/kg, Dolethal®; Vé-
toquinol E.V.S.A., Madrid, Spain). Eyes were immediately and sequentially tested after sacrifice, and the whole process lasted less than ten minutes (eye extraction, scleral cutting, pachymetry measurements, inflation, and indentation) to ensure minimum swelling. In addition, before clamping the sample into the experimental setup, it was stored in saline solution, and the same experienced researcher (Á.O.) ensured that the epithelium was intact. After eye enucleation, a circular area including the cornea and a scleral rim were cut off and placed in a metallic rig that was hermetically closed to avoid undesired pressure variations (the black dot in Figure 5.1.b-d). During the experiments, hydroxypropylmethylcellulose 2% was applied to maintain dehydration. Finally, all samples were prepared under physiological conditions, orienting the epithelium externally and the endothelium internally.

The inflation test was controlled by a water column (the blue dot in Figure 5.1.b-d). First, five cycles of inflation to 14.5 mmHg (average IOP of the rabbits before sacrifice; 20 cmH$_2$O) were performed to pre-condition the sample. Subsequently, two cycles from 0 to 42.5 mmHg (maximum desired IOP: 58.2 cmH$_2$O) were carried out. To avoid incorrect measurements, a pressure probe (the red dot in Figure 5.1.b-d) was set in a security loop to read pressure variations. The entire procedure was recorded using a synchronized stereo rig (the green dot in Figure 5.1.b-d) composed of two Prosilica GT1290 cameras with a Sony ICX445 EXview HAD CCD sensor. The sequence of black and white images (resolution of 1280x960, frame rate of 5 fps) was stored in raw format to avoid compression losses. The cameras were situated over the cornea to facilitate both cameras being able to cover the upper surface of the eye. The parallax obtained with the setup was close to 90°, which is the optimal parallax value that guarantees the highest accuracy of the measurement method. To establish the intrinsic parameters of the camera and its internal geometry, a priori camera calibration protocol was performed. A planar pattern method similar to Bouguet 2011 was applied. A small black dot was painted in the central point of the cornea and used as fiducial marker that was tracked during the experiment (see Figure 5.1.2.c). From the recorded video, a stereo pair of frames was selected for different levels of the IOP. The 3D coordinates of the central point were estimated using PhotoModeler digital photogrammetry software (PhotoModeler Scanner 2013®; Eos Systems Inc., Vancouver, Canada). Based on the change in these coordinates, the evolution of the total displacement was calculated for each IOP. Finally, the mechanical inflation response of the cornea was represented as the apical rise (i.e., apical displacement of the eye measured in mm) versus the variation in the IOP (i.e., inner pressure measured in millimeters of mercury, mmHg).

After the inflation test, the IOP was set to 14.5 mmHg (average IOP of the rabbits before sacrifice; 20 cmH$_2$O), and the indentation test was performed in each eye immediately after pressurization. Five load cycles (Newton, N) were applied on

15 Ortíllés et al. 2017a
16 Ni et al. 2011
the center of the cornea under displacement control. An Instrom 5548 microtester (Illinois Tool Works Inc., Glenview, USA) with a 5 N full-scale load cell and an 3 mm diameter indenter (i.e., a typical applanation tonometer) was used (the gray dot in Figure 5.1.b-d). The displacement rate was 0.5 mm/s, and the maximum displacement was $\delta_{\text{max}} = 1$ mm to reach an inversion of the corneal curvature (i.e., going beyond applanation to bending, see Ortillés et al. 2017b). To ensure contact between the tip and the cornea, the indenter is approached with a control in displacement (displacement rate of 0.5 mm/min) until the load cell provides a measure of $\pm 1$ mN. The mechanical indentation response was represented as the force opposing to the indentation (measured in newtons, N) versus the indentation displacement (measured in millimetres, mm).

**Astigmatic Keratotomy**

AK is an ocular refractive surgery that aims at reducing corneal astigmatism (i.e., the difference between the maximum and minimum curvature), modifying a more elliptic into a more spherical cornea. Four animals were intramuscularly anesthetized using a mixture of medetomidine (0.14 mg/kg, Medeson®; Uranovet, Barcelona, Spain), ketamine (20 mg/kg, Imalgene 1000®; Merial Laboratorios S.A., Barcelona, Spain) and butorphanol (0.3 mg/kg, Torbugesic®; Fort Dodge Veterinaria S.A., Girona, Spain). Topical anesthesia with tetracaine hydrochloride 0.1% and oxybuprocaine 0.4% eye drops (Colircusi Anestésico Doble®; Alcon Cusí, Barcelona, Spain) was also imparted. All surgeries were performed by the same corneal specialist (J.A.C.) in both eyes of each animal. From the corneal topography, the topographic axis was used to determine the treatment position, and the topographic cylinder measurement was used to define the length of the incisions. Two straight (transverse) astigmatic incisions of 6 mm were made and were located in a 7 mm diameter optical zone along the most curved meridian. The tissue was cut to an 80% in depth (320 $\mu$m) using a guarded diamond blade. All animals were treated post-operatively with a topical corticosteroid (prednisolone acetate, Pred-Forte®; Allergan S.A., Madrid, Spain) and a broad-spectrum antibiotic (bacitracin/neomycin/polymyxin B, Oftalmowell®; UCB Pharma S.A., Madrid, Spain) twice a day for a week. Ten days after the surgery, the surgery follow-up was carried out by measuring the corneal topography.

**Numerical Protocol: Inverse Characterization of Corneal Properties**

The optimization protocol uses an inverse finite element iterative algorithm (hereafter iFEM). iFEM seeks to minimize the difference between the experimental and
Methods for Characterising Patient–Specific Corneal Biomechanics

Figure 5.1: Experimental Protocol. (a) Mechanical response of the corneal stroma. Due to the physiological IOP, the anterior and posterior stroma are under normal tension (see the square and inverted triangle close to the white dot). When an indentation is applied, the cornea bends. Thus, the anterior stroma is compressed (the inverted triangle close to the solid black dot), and the posterior stroma is tensioned far from the normal range (the square close to the solid black dot); (b) Conceptual Diagram of the Experimental Protocol: The water column was for setting the IOP (blue), the pressure probe was for controlling the IOP (red), the vision system was for recording the apical rise during the pressurization (green), the Instron testing machine was for indenting (gray), and the metallic rig was for fixing the biological sample (black); (c) Expanded image of the biological sample fixed in the rig. A dotted pattern is used for videotracking the displacement field; (d) Complete experimental setup (each colored circle corresponds to the colored circle in the diagram presented in (b)).
numerical mechanical responses (inflation and indentation) by changing the material properties of the proposed strain energy function.

**Constitutive Equation**

The Demiray strain energy function\(^\text{17}\) (5.1b) was used to simulate the isotropic hyperelastic behaviour of the extracellular matrix, whereas the Holzapfel–Gasser–Ogden strain energy function\(^\text{18}\) (5.1c) was used to simulate the anisotropic behavior of the collagen fibers. The coupled strain energy functions, along with a penalty volumetric term (5.1a), were used to represent the anisotropic hyperelastic behavior of the cornea.

\[
\psi = \psi_D + \psi_{HGO} + \frac{1}{D} \cdot \left( \frac{I_{el}^2 - 1}{2} - \ln(I_{el}) \right) 
\]

\[
\psi_D = D_1 \cdot (e^{D_2 \cdot (I_1 - 3)} - 1) 
\]

\[
\psi_{HGO} = \frac{k_1}{2 \cdot k_2} \cdot \sum_{\alpha=1}^{N} \{e^{k_2(I_{4(\alpha \alpha)} - 1)^2} - 1\} 
\]

where \(D\) is the volumetric parameter, \(I_{el} = \det \mathbf{F}\) is the elastic volume ratio, \(D_1\) and \(D_2\) are the parameters of the isotropic term \(\psi_D\), \(I_1\) is the first invariant of the modified right Cauchy-Green tensor \(\mathbf{C} = J^{-2/3} \mathbf{C} = J^{-2/3} \mathbf{F}^T \mathbf{F}\), \(\mathbf{F}\) the deformation gradient, \(k_1\) and \(k_2\) are the parameters of the anisotropic term \(\psi_{HGO}\), and \(I_{4(\alpha \alpha)} = n_\alpha \cdot \mathbf{C} n_\alpha\) is the square of the stretch along the fiber direction \((n_\alpha)^2\). In contrast to the orthogonal distribution of collagen fibers in humans, the collagen fibers in New Zealand rabbits are disposed circumferentially\(^\text{19}\) (see Figure 5.2.b). The model assumes that collagen fibers bear load only under tension, while they buckle under compressive loading. Hence, only when the strain of the fibers is positive, i.e., \((I_{4(\alpha \alpha)} - 1) > 0\), do the fibers contribute to the strain energy function. This condition is enforced by the term \(\langle I_{4(\alpha \alpha)} - 1 \rangle\), where the operator \(\langle \cdot \rangle\) stands for the Macauley bracket, which is defined as \(\langle x \rangle = \frac{1}{2} (|x| + x)\).

The parameters that define the matrix term of the tissue \((D_1\) and \(D_2\)) and the parameters that define the behavior of the collagen fibers \((k_1\) and \(k_2\)) were the variables used by the optimization algorithm to represent the behavior of the cornea.

The Yeoh strain energy function\(^\text{20}\) was used to simulate the sclera (5.2).

\[
\psi_Y = \sum_{i=1}^{3} \frac{1}{D_i} (I_{el} - 1)^{2i} + \sum_{i=1}^{3} Y_{i0} \cdot (I_1 - 3)^i, 
\]

where \(Y_{10} = 810\) (kPa), \(Y_{20} = 56050\) (kPa), \(Y_{30} = 2332260\) (kPa), and \(D_i = 0.0\) (kPa\(^{-1}\)).

Although the sclera presents collagen fibers, these do not exhibit a clear organization far from the insertion of the optical nerve. Therefore, an hypothesis of isotropy

\(^{17}\) Demiray 1972

\(^{18}\) Holzapfel et al. 2000

\(^{19}\) Hayes et al. 2007, Winkler et al. 2015

\(^{20}\) Yeoh 1993
was assumed. In addition, the sclera played a secondary role in the simulations and was used to impose a more realistic boundary condition rather than to impose a displacement boundary condition.\textsuperscript{21}

\textit{Computational Finite Element Models: Indentation and Inflation Tests}

Two geometrical models were built. First, the average 1/4 symmetric model was built assuming an spherical cornea (see Figure 5.2.b) and an scleral strip of 2 mm. It was composed of 26,320 8-node linear hybrid hexahedral elements (C3D8H) and 30,537 nodes (91,611 degrees of freedom, D.O.F.). Second, the patient-specific model was built by transforming a geometrical template into the point cloud of the actual corneal coordinates.\textsuperscript{22} The template was composed of 63,361 nodes (190,083 D.O.F.) and 50,466 C3D8H elements. The indenter was composed of 2,345 8-node linear hexahedral elements (C3D8) and 2,995 nodes (8,985 D.O.F.).

The mesh chosen is fine enough to properly capture the contact between the indenter and the cornea and to provide an accurate record of the pressure, area, and forces measured at the tip. Regarding the boundary conditions, a restrained displacement was imposed at the scleral rim to mimic the clamping of the sample, and a uniform pressure was imposed on the inner surface to reproduce the IOP. The contact between the indenter and the cornea was modeled as a frictionless hard contact allowing separation.
Numerical-Experimental Protocol to Determine Corneal Properties

iFEM Optimization

The optimization algorithm (see Figure 5.3) was based on a constrained optimization and provided the upper and lower limits of the material properties. First, an iterative algorithm was used to identify the load-free configuration of the eye (IOP = 0 mmHg, hereafter referred to as the free-stress reference configuration) since the geometry characterized using the topographer is already pressurized at the IOP (average *in vivo* pressure, IOP = 14.5 mmHg). When the reference configuration was pressurized, the original shape of the cornea was recovered but included the pre-stress. Following the determination of the free-stress reference configuration, the simulation protocol was performed. Initially, the indenter was located far enough (i.e., 5 mm) from the ocular apex to avoid an accidental contact during the pressurization. The inflation procedure was simulated, departing from the free-stress reference configuration (IOP = 0 mmHg) by applying an IOP of 42.5 mmHg (5.6 kPa). The evolution of the apical rise with pressure was recorded (i.e., apical Rise vs pressurization mechanical response; see Numerical U-P in Fig. 5.4).

Subsequently, the indentation was simulated, and the evolution of the contact force during the displacement was recorded (see Numerical F-d in Fig. 5.4). As the material properties were modified in each iteration, the indenter needed to be repositioned depending on the location of the apex, which in turn depended on the material and IOP. The following two-step procedure was implemented:

1. A pressurization from the free-stress reference configuration to the *in vivo* physiological IOP (14.5 mmHg, or 1.93 kPa) was performed to determine where the apex will be (Figure 5.2.(a.1)). The indenter was then placed to ensure contact independent of the material parameters (Figure 5.2.(a.2)).

2. An 1 mm deep indentation was performed with a pressurization of 14.5 mmHg (Figure 5.2.(a.3)).

Finally, the mean squared error (MSE) between the numerical and the experimental curves was considered as the objective function. The total MSE (5.3) was the contribution of the MSE between the numerical and the experimental mechanical response for both experiments (indentation–1 and inflation–2).

\[
MSE = MSE_1 + MSE_2 \\
MSE_k = \frac{1}{n_k} \sum_{i=1}^{n_k} \left( \frac{N_{ik}}{\text{max}(E_k)} - \frac{E_{ik}}{\text{max}(E_k)} \right)^2
\]

where \(N_k\) is a vector containing the pointwise numerical response and \(E_k\) is a vector containing the pointwise experimental response. The \(MSE_k\) is normalized by the maximum of the experimental response (i.e., \(\text{max}(E_k)\)) and weighted by the

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Figure 5.3: Modular Design of the Optimization Algorithm. The iterative loop of the algorithm consists of a pre-stress algorithm (Stress-Free Config. in blue), the indenter relocation depending on the initial pressurization and material properties (Indenter Relocation in blue), the indentation FE simulation (INDENTATION in green), the inflation FE simulation (INFLATION in green) and the computation of the objective function \( \text{MSE} = \text{MSE}_1 + \text{MSE}_2 \) (5.3). The optical quality of the cornea is predicted after the AK simulation (surgery in green).
number of points of the curve $n_k$. Hence, numerical problems derived from the difference in the order of magnitude of the variables (i.e., $1e-2$ for indentation and $1e0$ for the inflation) were avoided.

All the finite element computations have been carried out using commercial Abaqus software (Dassault Systèmes, Simulia). To solve the optimization problem, Matlab (Matrix Laboratory, Mathworks) has been used.

**Validation of the Protocol: Prediction of Astigmatic Keratotomy**

Ocular refractive surgery is used to validate the calibrated mechanical model of the cornea after the inverse optimization. Using only the optimal material properties of the cornea, the patient-specific corneal surgery is simulated. If the numerical optical outcomes match the experimental optical outcomes, then the protocol is providing a well-calibrated set of material properties, including both corneal behaviors.

**Computational Finite Element Model of the Surgery**

The patient-specific and average models (see in Figure 5.2.c) were composed of 50,466 C3D8H and 63,361 nodes. A symmetry displacement condition along the optical axis was considered on the scleral equatorial plane (i.e., no displacement along the optical axis). The IOP was simulated as an uniform pressure imposed on the inner surface of the eyeball. The surgical incisional procedure was simulated using a contact surface between both faces of the cut (see the area highlighted in red in Figure 5.2.c). Once the eye was pressurized, the contact was released to simulate the aperture of the corneal tissue. Regarding the constitutive equation, the optimal set of material properties ($D_1$, $D_2$, $k_1$, and $k_2$) identified after the optimization step was used to simulate the AK surgery.

**Optical Quality of the Cornea: Metrics of the Validation**

The optical quality of the cornea was used as criterion to validate the model. However, the optical algorithms within the commercial devices (e.g., MODI) are partially unknown, and it was not possible to evaluate the numerical and experimental results using the same metric. Thus, an in-house optical software was implemented to consistently compare the experiment to the simulation. The cylindrical ($\text{Cyl}$) and spherical ($\text{Sph}$) power of the wavefront aberration of the ocular system was used to assess the optical quality.

First, the corneal surface was fit to a 12th order Zernike polynomials\(^{24}\) (see the definition in Appendix D.1). The reconstruction error was lower than 1 $\mu$m (results 24 Dai 2008, Lakshminarayanan and Fleck 2011).
not shown). As complementary information, the refractive power of the cornea was computed using the tangential and sagittal curvature of the surface.\(^{25}\) Second, the wavefront aberrometry was computed. In a perfect optical system, outgoing light forms a sphere, and the wavefront is zero. However, in a real system with small imperfections, the wavefront slightly departs from the reference sphere, resulting in optical aberrations. The wavefront aberration was obtained as the difference in optical path length between the chief ray (central ray) and the marginal rays (peripheral rays). To compute the difference in the geometrical path, a ray-tracing algorithm was used.\(^{26}\) Briefly, a source of light located at infinity emitting ray beams parallel to the optical axis of the cornea is considered. The vectorial Snell law was applied to the corneal surface to compute the propagation of light.\(^{27}\) The difference in geometrical distance between each medium was computed beamwise to obtain the optical path difference. Finally, the wavefront aberration was fit to a Zernike polynomial expansion. The resulting Zernike coefficients were directly related to the spherical and cylindrical power (see the definition in Appendix D.5) of the ocular system.\(^{28}\)

The ray-tracing algorithm was validated using OSLO (Optics Software for Layout and Optimization, Lambda Research Group, results not shown). Since MODI provides only the anterior surface of the cornea, and thanks to the uniformity of the corneal thickness in New Zealand rabbits, only the refraction of the external surface was taken into account. The refraction index of the cornea was assumed as \(n = 1.3375.\)

5.3 Results and Discussion

Geometrical characterization of the tested eyes showed a uniform corneal thickness (380 ± 2 \(\mu m\)) with similar vertical (\(R_v\)) and horizontal (\(R_h\)) radii: 7.114 ± 0.204 and 7.038 ± 0.196 mm, respectively. Although the actual corneal geometry is slightly ellipsoidal (2.24% difference between \(R_v\) and \(R_h\)), a spherical cornea with a curvature radius of 7.1 mm was used in the average numerical model. In addition, the in-house optical algorithm gives a dioptric map that is in good agreement with those provided by MODI (see below in Fig. 5.6.a-b).

Regarding the mechanical experiments (see the mean and dispersion in Fig. 5.4), the indentation tests showed an average final force of 0.43 ± 0.15 mN (in the range of previously reported experimental in vivo indentation tests, Ortillés et al. 2017b) and the inflation tests showed an average final apical range of 1.1 ± 0.1 mm (in the range of previously reported experimental ex vivo inflation tests, Ni et al. 2011).

The iFEM algorithm was executed five times using different initial seeds to verify the existence of local minima. Although few local minima were present, the final pre-
Figure 5.4: Experimental and Numerical Mechanical Response of the Cornea. (a) Results of the indentation experiments. The force reaction (N) is measured during the controlled indentation (mm) to a depth of 1 mm; (b) Results of the inflation experiments. The apical rise (mm) is measured during the controlled pressurization of the eyeball to 42.5 mmHg. Shaded areas (blue/red) represent the dispersion, and the solid line (blue/red) represents the average of the experimental results. Gray dots represent the variability of the numerical response (indentation/inflation) with respect to the material variations.

diction was always inside the experimental range (results not shown). The most repeatable solution was achieved in 84 iterations with an MSE of 5.29e-3. The optimal set of material properties is $D_1 = 0.224$ (kPa), $D_2 = 25$ (–), $k_1 = 2.148$ (kPa), and $k_2 = 255.144$ (–). The mechanical response to inflation is much more sensitive to material perturbations than the response to indentation (see the gray dots in Figure 5.4). The inflation experiments are carried out by loading the free-stress reference configuration (IOP = 0 mmHg), whereas the indentation experiments are performed by departing from a pre-stressed configuration (IOP = 14.5 mmHg); however, the sensitivity of the mechanical properties of both experiments is mainly dependent on the stress state. During inflation, the corneal thickness (CT) exhibits a uniform biaxial tensile stress state (see Fig. 5.5), where the ground matrix and the collagen fibers are contributing to load bearing. By contrast, during indentation, the CT displays a heterogeneous bending stress distribution, where part of the fibers do not contribute to load bearing, and thus, the ground matrix must resist the compression, while the posterior collagen fibers are much more stretched than they are in a physiological state (see Fig. 5.5). In addition, since there is an inverse cubic relationship between displacement and thickness during bending, 30 the material stiffness does not dominate the physics of the problem. This explains the lower sensitivity of the indentation test to material alterations compared to the inflation test. Nevertheless,
it is also important to note that if inflation experiments were applied by departing from a pre-stressed configuration of the cornea, the dispersion (not the sensitivity) of the curves would be lower. The comparison between the initial and final slopes of the inflation curves supports that the greatest source of dispersion arises during the beginning of the inflation experiments (IOP < 5 mmHg) when the cornea is not fully stretched. Finally, both experimental curves, inflation (in red in Figure 5.4) and indentation (in blue in Figure 5.4), were simultaneously fit with the same set of material parameters, showing the capability of the proposed model to reproduce both behaviors.

![Figure 5.5: Stress-stretch behavior of the corneal tissue in polar coordinates (rr – radial, tt – tangential) during an indentation. (left panel) Behavior of the anterior and posterior stroma departing from the free-stress reference configuration (IOP = 0 mmHg, white triangle) and reaching the natural pre-stretch (IOP = 14.5 mmHg, white circles) during the indentation (δ = 1 mm, black squares and circle). Anterior stroma (solid and dashed blue lines) goes from the natural tensile state due to the pre-stress (see white dot) to a non-physiological state of compression. The posterior stroma (solid and dashed red lines) converts from the natural pre-stress state to a higher tensile state (only traction). Moreover, during indentation, the anterior stroma behaves isotropically (λ < 1, dashed and solid lines coincide) since the fibers are not contributing to load bearing. By contrast, in the posterior stroma, we can differentiate a higher resistance in tangential direction (tt direction) where the fibers lay (dashed red lines) rather than in radial direction (rr direction) that is orthogonal to the fibers; (right panel) FE simulation of the indentation (δ = 1 mm). Only compression (blue) and traction (red) are differentiated. It can be clearly observed that the anterior stroma functions under compression, whereas posterior stroma functions under tension.

Outcomes of the surgery indicate that the average models are not the best option to reproduce the optical features of the cornea (rows 4 and 5 in Table 5.1). Optics is purely determined by the geometry of the cornea, while geometry depends on IOP and material stiffness. Hence, only patient-specific models are reliable in terms of refractive outcomes. Although all specimens presented the same trend, for the sake of simplicity all results correspond to the specimen with the most representative bow-tie pattern associated with astigmatism (see in Fig. 5.6.a–b).

The optical features of the actual geometry (rows 2 and 3 in Table 5.1) and the patient-specific simulation (rows 6 and 7 in Table 5.1) are given for a circular area of 3 mm in radius (i.e. the optical zone corresponding to the physical pupil of the system). The models are able to reproduce the overall optical quality of the cornea after the AK surgery. The prediction of the cylindrical power ($C_{yl}$) is in good agree-

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Table 5.1: Experimental (Exp.) and numerical (average, Avg.; patient-specific, PS.) corneal optics before (Pre.) and after (Post.) the AK surgery. Zernike coefficients ($z_{nm}^2$) in microns. Cylindric (Cyl) and spherical power (Sph) in diopters. Astigmatic angle ($\phi$) measured with respect the nasal-temporal axis (horizontal axis) in degrees.

<table>
<thead>
<tr>
<th></th>
<th>$z_{2}^{-2}$</th>
<th>$z_{0}^{2}$</th>
<th>$z_{2}^{2}$</th>
<th>Sph</th>
<th>Cyl</th>
<th>$\phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. Pre.</td>
<td>-0.97</td>
<td>-22.79</td>
<td>-0.95</td>
<td>10.8</td>
<td>-0.9</td>
<td>23</td>
</tr>
<tr>
<td>Exp. Post.</td>
<td>0.44</td>
<td>-25.5</td>
<td>-7.6</td>
<td>13.7</td>
<td>-4.8</td>
<td>2</td>
</tr>
<tr>
<td>Avg. Pre.</td>
<td>-0.89</td>
<td>31.02</td>
<td>-0.75</td>
<td>-12.8</td>
<td>-0.7</td>
<td>25</td>
</tr>
<tr>
<td>Avg. Post.</td>
<td>-6.6</td>
<td>28.8</td>
<td>-5.45</td>
<td>-9.64</td>
<td>-5.1</td>
<td>25</td>
</tr>
<tr>
<td>PS. Pre.</td>
<td>-1.94</td>
<td>-23.01</td>
<td>-0.96</td>
<td>10.7</td>
<td>-1.3</td>
<td>32</td>
</tr>
<tr>
<td>PS. Post.</td>
<td>-6.76</td>
<td>-26.45</td>
<td>1.99</td>
<td>13.7</td>
<td>-4.4</td>
<td>-37</td>
</tr>
</tbody>
</table>

ment with experiments (+0.4 D and -0.4D pre- and post-operatively). Similarly, the spherical power (Sph) is in good agreement with the experiments (-0.1 D and 0 D pre- and post-operatively). Surprisingly, despite using a patient-specific geometry, the optical features of the pre-surgical numerical model do not match the actual optical parameters of the pre-surgical experimental eye. This is explained by the impact of the pre-stress algorithm on the initial geometry. Due to its iterative nature, the patient-specific geometry is recovered with a maximum error of approximately 2 micron (i.e. convergence limit of the algorithm). Since the optical features are very subtle, small perturbations of the geometry will lead to different optical values. In this vein, the simulated Zernike coefficients neither match the actual post-surgical Zernike coefficients of the experiment. Although not all the optical features are accurately predicted, numerical models predict the overall dioptric correction, showing the same trend as the experiments: an increase in spherical and cylindrical power, as qualitatively expected due to the corneal physiology of the rabbit. Since the initial configuration of the cornea of the rabbit is almost spherical, a clear astigmatism is induced. The retinal spot diagram supports this fact (Figure 5.6.c–d). After the AK surgery, the pre-surgical circular pattern, associated to a spherical cornea, changed to a post-surgical elliptic pattern, associated with an astigmatic cornea.

5.4 Conclusion

A numerical-experimental protocol to obtain the material properties of the cornea has been proposed. The novelty of this protocol relies on minimizing two mechanical responses simultaneously. The mechanical responses reproduce both the physiological condition of the eye (inflation) and the non-physiological state induced by tonometers in the clinic. In addition, the experimental protocol allows analysis of a biological sample without repositioning (i.e., avoiding the need to move the sample between measurements). The numerical optimization process reproduces the experimental protocol. Thanks to its automatization, it can be used as a non-supervised process. Despite few local minima being found, the set of material parameters obtained by reproducing the surgery were in good agreement with those from the experiments. The single-thread optimization process took approximately 100 iterations to find the optimum values. The bottleneck of the optimization
Figure 5.6: Ray-tracing results for the third specimen. (a) Post-surgical dioptrés map provided by the MODI device; (b) Post-surgical dioptrés map provided by the in-house ray-tracing software; (c–d) Retinal spot diagram of the numerical model before (c) and after (d) surgery. After the AK surgery, a more slanted pattern is obtained, demonstrating that astigmatism is induced.
is the number of finite element simulations required on each iteration (i.e., 10 FE simulations) and the time of each iteration (i.e., 2 hours per iteration). A common commercial computer (i.e., 8 i7 cores with 12 GB of RAM) performed the whole iteration process in approximately 7 days. The process cannot be parallelized in a straightforward manner.

Finally, the protocol allows the fitting of a numerical model that represents both behaviors of the cornea: tension and compression. This fact is of key importance since the majority of the clinical tests and surgeries subject the cornea to both stress states to a certain degree. Proper characterization of both behaviors enables the prediction and qualitative assessment of, for example, ocular refractive surgeries. In this work, we used a real refractive surgery (astigmatic keratotomy) to validate the optimal set of material properties. Using only the material properties provided by our protocol (i.e., the properties minimized using the inflation and indentation tests), we could numerically predict the patient-specific optical outcomes of the real surgery with a reasonable degree of accuracy (error of ≈ 0.1 D in spherical power and ≈ 0.5 D in cylindrical power), showing the potential applicability of the present research.

The study is not exempt from limitations. Regarding the computational models, the average spherical model cannot reproduce the optical outcomes. The inclusion of patient-specific models demonstrate the importance of obtaining an overall dioptic correction close to the experiments. However, the subtlest optical features (i.e., corneal aberrations) are not properly reproduced. The phenomenological macroscopic strain energy function can help to explain this lack of sensitivity. Including the microscopic features reported by Winkler et al. 2015 and Krüger et al. 2011 could help to reproduce a variational stiffness that allows for better deformation mapping. In addition, rabbits exhibit two different degrees of collagen organization within the stroma. Those fibers close to the posterior stroma are more organized, while those close to the anterior stroma display a large anastomosis (i.e., branching between the collagen fibers), partially losing the organization. Hence, anisotropic behavior is predominant in the posterior stroma, whereas the anterior stroma shows more isotropic behavior. In this regard, the cornea would be more locally compliant in the area surrounding the incisions, whereas our models have the same stiffness through the corneal thickness. In addition, viscoelastic effects are not taken into account. The velocity of the tests was about 30 second in all cases, and therefore, the viscoelastic effects were assumed to have a low impact. However, the relaxation of the tissue is of great importance when modeling surgery. When the incisions are performed, a new instantaneous equilibrium is achieved due to the stabilization of the IOP. Our models predict this immediate change but do not account for the change in curvature associated with the relaxation of the tissue after the surgery (i.e., after 10 days). Additionally, the stiffening due to the healing

\[ \text{Simo } 1987 \]
process was not considered. Although its contribution seems small, viscoelasticity plays a non-negligible role in the characterization of the optics based on Zernike polynomials. Finally, one of the most important limitations of this methodology is the difficulty associated with extending it to humans. The protocol needs to build a reliable database of \textit{ex vivo} inflation experiments. Then, it, along with \textit{in vivo} indentation measures, could be used to characterize the properties of the human cornea.

The proposed optimization protocol is the first that minimizes both mechanical responses of the cornea. This will help to avoid an ill-posed calibration of the corneal parameters.\textsuperscript{33} Furthermore, the modular design allow the incorporation of more complex features (i.e., viscoelasticity or microstructure) without modifying the layout. Moreover, the set of material parameters identified by the optimizer could be applied to additional simulations, such as intracorneal ring segment (ICRS) implantation or laser-based refractive surgery simulation.
6 Fluid-Structure Interaction Simulation of a Non-Contact Tonometry

Simplicity is a great virtue but it requires hard work to achieve it and education to appreciate it. And to make matters worse: complexity sells better

Edsger W. Dijkstra

This chapter assesses in the necessity of fluid-structure interaction simulations to numerically reproduce non-contact tonometries. We build a 2D axisymmetric model of a porcine cornea, and perform different simulations: pure mechanical (Abaqus), and fluid-structure interaction (LS-DYNA) simulations. The effect of different features such as boundary conditions, or internal structures is studied

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### 6.1 Introduction

Non-Contact, or bidirection applanation, tonometers (NCTs) are used in Ophthalmology in a daily basis (i.e. Ocular Response Analyzer, ORA, Reichert, Depew, NY, USA; and CorVis ST, OCULUS Optikgeräte GmbH, Wetzlar, Germany). These devices aimed at determining the intraocular pressure of the eye (IOP) without being physically in contact with the cornea as contact tonometers do (e.g. Goldmann Applanation tonometry, GAT), and with less influence of the thickness. As working principle, a corneal deformation is induced by exerting a violent short air pulse (i.e. total duration of \( \approx 30 \text{ ms} \)). Meaning that an air jet between 120 to 150 m/s is applied, with a pressure peak between 10 to 15 kPa (i.e. 75 to 115 mmHg, or 5 to 8 times the normal value of intraocular pressure). Besides, the corneal kinematics goes through 5 main stages: the *initial steady position* from where the cornea goes inwards, the *first applanation* where a 3-mm central area of the cornea is analyzed to determine how much is flattened, the *maximum concavity* where the cornea reaches its highest deformation amplitude before going outwards, the *second applanation* and, finally, the *recovery position*. CorVis ST presents two main distinguishing features: first, corneal imaging is recorded by a Scheimpflug camera during the deformation (4,330 frames per second) and, second, an independent 'fixed' pressure is always applied, forcing the cornea to go beyond the first applanation to the concavity. On the contrary, ORA does not record corneal imaging, but uses infrared light to detect the first applanation as trigger to cut off the air pulse. However, as there is a time delay, the cornea will always slightly overpass the first applanation.\(^2\)

Different biomarkers are extracted depending on the device and the kinematic stage analyzed. Both devices provide the first (and second) applanation length (and time), or different corrected IOP measurements that are reported to be more accurate than GAT measurements. In particular, CorVis ST provides with the maximum deformation amplitude (and time), the corneal central thickness (CCT) derived from corneal imaging, and the corneal speed over time (see in Fig.6.1.b). ORA's differential value relies on the Corneal Hysteresis (CH, see in Fig.6.1.a), which aims at shedding light into the corneal viscoelastic properties. The CH is the difference between the air jet pressure, also called plenum pressure, at the first applanation time (P1), and the plenum pressure at the second applanation time (P2). Average population values of the CorVis ST biomarkers have been reported by Hon and colleagues (see below in Table 6.2) with a great intraseesion repeatability, only including normal corneas (i.e. patients without ectatic or glaucoma pathologies).\(^3\) In this vein, on a former study Luce et collaborators reported that the corneal hysteresis range for healthy patients is 9.3 ± 1.4 mmHg.\(^4\) Nevertheless, several authors have reported significant reduced CH values for glaucomatous,\(^5\) and post-laser

\(^{2}\) Piñero and Alcón 2014, 2015  
\(^{3}\) Hon and Lam 2013  
\(^{4}\) Luce 2005, 2002  
\(^{5}\) Abitbol et al. 2010
refractive surgeries eyes.\textsuperscript{6} Not only that, for keratoconic corneas (i.e. a non-inflammatory disease that causes the physiological disruption of the collagen fibers network), CH has been demonstrated to be a poor discrimination parameter with respect to normal corneas,\textsuperscript{7} whereas air pressure levels and times are significantly lower and shorter as well.\textsuperscript{8} Eventually, the mechanical properties of the corneal tissue, which is a key factor in the assessment of collagen-related diseases, are not provided directly by NCTs.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6_1.png}
\caption{Signals of commercial NCTs. (a) Schematic representation of ORA’s signal. Applanation signal (red line), air jet pressure (green line). Corneal Hysteresis is the difference between applanation pressures ($CH = P_1 - P_2$); (b) CorVis ST graphic interface: (b.1) Deformation amplitude over time, (b.2) Applanation length over time, (b.3) Velocity of the cornea over time.}
\end{figure}

Optimization techniques have been recently applied to blend clinical data and computation so as to retrieve the mechanical properties of the corneal tissue.\textsuperscript{9} Generally, these inverse optimization techniques make use of finite element (FE) simulations (quasi-static, or dynamic), where the experiment is mimicked assuming certain hypothesis. Regarding the tissue behaviour, hyperelastic anisotropic strain energy functions are usually considered,\textsuperscript{10} coupling the hyperelastic isotropic behavior of the ground substance (i.e. extracellular matrix), and the hyperelastic anisotropic behavior of the collagen fibers embedded on it. But not only the material behavior must be properly reproduced, the conditions of the experiment are also of key importance. In this regard, a differentiation can be done between the extraocular and intraocular boundary conditions. On the one hand, the external surrounding media are not included, or are assumed to exert an uniform pressure over the organ surface. On the other hand, the internal physical structures (i.e. lens and ciliary muscles) are usually neglected, whereas the aqueous and vitreous humours are assumed as internal constant pressures. Finally, a load condition as the NCT’s air pressure is approximated as a gaussian-shaped pressure distributed over the corneal surface.\textsuperscript{11} All this assumptions can easily lead to overestimated post-optimization corneal stiffness, or to erroneous kinematics, deformation patterns, and stress distributions.

Fluid-structure interaction (FSI) problems are the natural evolution of the pure mechanical simulations in simulating complex biological systems. The underlying axiom is to couple the deformable (hyper)elastic solid problem with the internal (or

\textsuperscript{6} Shah and Laiquzzaman 2009, Kamiya et al. 2009

\textsuperscript{7} Fontes et al. 2010, Galletti et al. 2012

\textsuperscript{8} Schweitzer et al. 2010

\textsuperscript{9} Girard et al. 2009a,b,c, Nguyen and Boyce 2011, Lago et al. 2015

\textsuperscript{10} Gasser et al. 2006, Pandolfi and Holzapfel 2008, Ariza-Gracia et al. 2016b,a

\textsuperscript{11} Sinha Roy et al. 2015, Ariza-Gracia et al. 2016a
external, or both) surrounding fluids, transferring (interpolating) the loads and displace-
ment fields at the contact surfaces. In this exchange of information, the fluid can apply a pressure over the solid that will result in a deformation or, vice versa, a deformation of the solid will displace the fluid. The real challenge is that this phenomenon usually occurs simultaneously. To solve coupled simulations there are two main methods: the direct, and the load transfer methods. In general, the direct method is not used in FSI problems since the stiffness matrices (fluid and solid) are vastly different, and could result in an ill-posed problem. The load vector method involves sequential iterations between both problems, e.g. first the fluid is solved to apply a load to the solid, the meshes updated, and the fluid re-iterated to continue the analysis till the convergence is achieved. The structural dynamics equation is generally formulated as,

\[ M \frac{\partial^2 u}{\partial t^2} + C \frac{\partial u}{\partial t} + Ku = F_{\text{Solid}} + F_{\text{Fluid}} \]  

(6.1)

where \( M \) is the structural mass matrix, \( C \) is the structural damping matrix, \( K \) is the structural stiffness matrix, and \( u \) is the displacement field (with its derivatives with respect to time), \( F_{\text{Solid}} \) is the load vector applied on the solid, and \( F_{\text{Fluid}} \) is the fluid pressure over the solid that is interpolated at the surface. In the case of NCTs, the external fluid pressure will be applied due to the air-jet \( (F_{\text{Fluid}}) \), but also the internal load due to the IOP should be treated as an inner pressurized fluid \( (F_{\text{Solid}}) \). Therefore, the eyeball acts as a solid coupled at the same time with internal and external fluid media.

Few FSI simulations involving the eye have been presented: the effect of blunt (or blast) impacts in eye injuries,\(^{14} \) the simulation of the iris displacement due to glaucomatous changes in IOP,\(^{15} \) or the attempts of correlating the IOP with the vibrations of the eye.\(^{16} \) Concerning the simulation of NCTs, some authors approximated the pressure profile exerted over the cornea by means of Computational Fluid Dynamics (CFD) simulations, but subsequently used a structural solution.\(^{17} \) In this regard, Roy et al. justified neglecting FSI simulations in non-contact tonometers since the shear pressure was several orders of magnitude smaller than the normal pressure over the eye.\(^{18} \) Currently and to the best of our knowledge, no FSI simulation of NCTs has been carried out yet.

At this point, an essential question arises: Is it important to use FSI simulations to accurately simulate NCTs? Or, could FSI simulations be substituted by pure mechanical simulations with an acceptable accuracy? And, in affirmative case, under what conditions does this substitution remain valid? Hence, the goal of this study is to develop a 2D axisymmetric FSI simulation of a general NCT test, and to compare under what load and boundary conditions a mechanical simulation can achieve similar results.
In order to do that, the same mechanical model (mechanical properties, and mesh definition) is simulated using LS-DYNA Release 9.0 (LSTC, Livermore CA, USA and ANSYS, Inc., Canonsburg PA, USA) and Abaqus v6.11 (Simulia, Dassault Systèmes). The geometry of the axisymmetric model is based on an average porcine cornea. Prior to the analysis, and although the material model is not the scope of the present investigation, the material calibration is performed using mechanical simulations (not FSI, due to its computational cost), in order to set a material behavior within the experiments reported for porcine corneas.\textsuperscript{19} The FSI simulation, accounting for the internal structures and the humors as fluids, is used as ground truth against which all the mechanical simulations are compared. Using only the mechanical approach (Abaqus), three different numerical tests are carried out to discern the best simulation strategy. First, the difference between applying a quasi-static simulation, or a dynamic simulation. Second, the difference between considering the aqueous and vitreous humors as an internal uniform pressure (DSLOAD), or a hydrostatic pressure (Fluid Cavity). Third, the difference between including or not the crystalline and the ciliary muscles. Finally and using the best computational approach, a simulation of the most relevant clinical biomarkers (CH, first and second applanation lengths and times, and maximum deformation amplitude) provided by CorVis and ORA is carried out to show the model's performance on reproducing NCTs.

\subsection{Material and Methods}

First, the common features (structural mesh, and mechanical properties) to all simulations are introduced. Second, all the numerical tests that are proposed to check the influence of internal structures, load conditions, and solving algorithms are presented so as to provided with a better follow-up of the different boundary conditions addressed in the subsequent sections. The final section gathers the description of the application of the best simulation strategy to reproduce the CorVis ST test.

\textit{Computational Model: Mesh and Mechanical Properties}

An axisymmetric model of an average porcine eye was used including the cornea with an average thickness of 850 microns, the sclera with an average thickness of 1 millimeter, the lens (or crystalline), and the ciliary muscles (see all measures in Fig.6.2.a-b). A mesh sensitivity analysis of the structural mesh was carried out in LS-DYNA to determine the best trade-off between computational time and accuracy (results not shown). All the simulations accounted for the same structural mesh composed of 1,073 nodes, and 957 4-nodes axisymmetric elements. Although porcine corneas present a more circumferential pattern of collagen fibers

\textsuperscript{19}Boschetti and Pandolfi 2012, Kling et al. 2014b
than humans, where the fibers are disposed more orthogonally, all involved tissues were considered as incompressible hyperelastic isotropic (cornea, sclera, and muscles), or elastic isotropic (crystalline) for the sake of simplicity, and since our objective is to compare both simulations and not the material behavior. A Demiray strain energy function (SEF) was used to represent the corneal behavior,

$$
\psi_D = D_1(e^{D_2(I_1-3)} - 1) + \frac{1}{D_i}(J_{el} - 1)^{2i}
$$

where $D_1$ (MPa) and $D_2$ (–) are the material parameters fitted to determine the tissue behavior, $D_i$ (MPa$^{-1}$) determines the compressibility of the material ($D_i = 10^{-7}$, to force the incompressibility), $J_{el}$ is the elastic volume strain, and $I_1$ is the first invariant ($tr(\tilde{C})$) of the modified right Cauchy-Green tensor ($\tilde{C}$). The mechanical parameters ($D_1$, $D_2$) used in the simulations were obtained by means of a basic optimization procedure using our mechanical gold standard simulation (see case 6 in Figure 6.3, and a more in depth discussion in 6.2, Abaqus Explicit simulation with internal structures and fluid cavity). A sequential grid-search of the material parameters was carried out to get a set of parameters that reproduces the average response of ex vivo inflation experiments and ex vivo NCTs tests. First, an area of interest (minimum) is detected in the initial grid-search. Second, a finer grid-search in the neighborhood of the first minimum is used to obtain the set of material parameters that minimizes both experiments. The optimized material parameters are $D_1 = 7.5563 e - 5$ (MPa) and $D_2 = 99.225$ (–) with a mean squared error (MSE) of $\approx 5e-3$ mm (see in Figure 6.2.e).
The sclera presents a random distribution of fibers far from the insertion of the optical nerve, then a Yeoh SEF was used to represent the scleral behavior.

\[
\psi_Y = \sum_{i=1}^{3} Y_{i0}(I_1 - 3)^i + \sum_{i=1}^{3} \frac{1}{D_i}(I_{el} - 1)^{2i}
\]  \hspace{1cm} (6.3)

where \(Y_{i0}\) (MPa) are the material parameters fitted to determine the tissue behavior, and the remaining parameters stand for the same definition as in the Demiray SEF. The reported material parameters used are: \(Y_{10} = 0.810\) (MPa), \(Y_{20} = 56.05\) (MPa), \(Y_{30} = 2332.26\) (MPa), \(D_i = 1.25 \cdot 10^{-6}\) (MPa\(^{-1}\)).

Finally, the lens (\(E = 1.45\) MPa, \(\nu = 0.47\)) and the muscle (\(E = 0.35\) MPa, \(\nu = 0.47\)) are assumed to be linear and quasi-incompressible.

Summary of Numerical Experiments

The numerical experiments (see Figure 6.3) proposed to discern the impact of different features in the outcomes of the simulations are,

**Case 1** Mechanical quasi-static simulation (Abaqus) without internal structures, and humors as uniform pressure (DSLOAD). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations).

**Case 2** Mechanical quasi-static simulation (Abaqus) with internal structures, and humors as uniform pressure (DSLOAD). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations).

**Case 3** Mechanical dynamic simulation (Abaqus) without internal structures, and humors as uniform pressure (DSLOAD). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations).

**Case 4** Mechanical dynamic simulation (Abaqus) with internal structures, and humors as uniform pressure (DSLOAD). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations).

**Case 5** Mechanical dynamic simulation (Abaqus) without internal structures, and humors as hydrostatic pressure (Fluid Cavity). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations).

**Case 6** Mechanical dynamic simulation (Abaqus) with internal structures, and humors as hydrostatic pressure (Fluid Cavity). Air is approximated as a bell-shaped pressure distribution over the cornea (retrieved from CFD simulations). Due to computation cost, and as we believe this is the closest simulation to the FSI simulation, the calibration of the material model is carried out using this simulation. Hence, it is the *mechanical gold standard* simulation.
Case 7 Fluid-Structure Interaction simulation (LS-DYNA) with internal structures (crystalline and ciliary muscles), and humors as uniform pressure. Air is simulated as a real fluid exerted through a nozzle separated from the cornea.

Case 8 Fluid-Structure Interaction simulation (LS-DYNA) with internal structures (crystalline and ciliary muscles), and humors as fluids. Air is simulated as a real fluid exerted through a nozzle separated from the cornea. This simulation is considered the closest simulation to the reality and, thus, the real gold standard to achieve.

Apart from comparing the maximum displacement of the corneal apex for all the simulations, 4 different tests are carried out to compare the whole corneal profile (see Figure 6.3). First, we compare the difference between using a quasi-static solver and a dynamic solver (Test 1). Second, we compare the difference between simulating the humors as a constant pressure or as a hydrostatic cavity allowing for the increment of pressure (Test 2). Third, we compare the difference between accounting for the internal structures or not (Test 3). Fourth, we compare the most complete mechanical simulation with respect to the analogous FSI simulation (Test 4).

Definition of the Simulation: Abaqus

Due to the axisymmetry of the model, a kinematic boundary condition of symmetry is set along the vertical axis so as to restrain the horizontal displacement, but to allow the vertical displacement and the rotation. Besides, a symmetry condition in
the scleral plane (horizontal axis) is set to allow the radial expansion of the eyeball, but to prevent the vertical displacement (see in Fig. 6.2.b).

Regarding the air pulse of the NCT, a CFD simulation (LS-DYNA) with a rigid cornea was carried out to determine the approximated gaussian-shaped distribution of the pressure over the cornea (see in Fig. 6.2.c). Afterwards, the profile was applied element-wise as a distributed pressure applied normally to the surface (DSLOAD). The peak of the pressure profile corresponds to 9 kPa, and spreads beyond the corneal limits (i.e. 6 mm in radius).

To simulate the aqueous and vitreous humors, two different strategies were analyzed,

1. Distributed Surface Load (DSLOAD). In this traditional approach, both fluids are considered to maintain a uniform constant pressure over the inner walls of the eyeball. In this boundary condition, the pressure remains constant along all the simulation. The intraocular pressure was set to a normal value of 15 mmHg (i.e. 2 kPa).

2. Hydrostatic Pressure (Fluid Cavity). Abaqus allows representing fluid-filled cavities under hydrostatic conditions, coupling the deformation of the fluid-filled structure and the pressure exerted by the contained fluid on the boundary of the cavity. The key point is that allows simulating pressurized vessels with constant volume, but accounting for the increment of pressure due to the compression of the cavity. The cavity is defined by a reference node (see $R_{\text{ANT}}$ and $R_{\text{POST}}$ in Fig. 6.2.b) in which the boundary condition is applied (i.e. pressure, or the mass rate of fluid), and by the surface defined by the faces of the surrounding elements. The fluid properties corresponds to water in normal conditions (incompressibility, no thermal expansion, and density of 1000 kg/m$^3$). This methodology must be applied in two steps. First, the cavity is pressurized applying the nominal value of 15 mmHg (i.e. constant pressure, variable volume). Second, the cavity is isolated to keep an isochoric process, allowing the pressure to decrease depending on the deformation of the cavity. This feature is essential since it will allow to understand (and quantify) the pressure in the anterior chamber during a NCT, and it will represent a more realistic boundary condition for the NCT’s simulation.

The same time steps are used in all simulations,

**Step 1** Pressurization of the eyeball. Duration of the step: 100 ms. The load is applied as a ramp during the step and kept constant during the subsequent step.

**Step 2** NCT’s air pulse. Duration of the step: 50 ms. The entire air pulse process
lasts 30 ms, with a subsequent resting phase of 20 ms. Within the air pulse, the load (0 to 15 ms) and unload (15 to 30 ms) processes are linearly applied.

Concerning the material behavior, the in-built Abaqus Yeoh SEF was used for the sclera and the muscles, whereas the Demiray SEF precised of a user subroutine definition. First, to carry out the quasi-static simulations a UHYPER subroutine was implemented, and axisymmetric 4-nodes elements with hybrid formulation (CAX4H) were used. Second, to carry out the dynamic explicit simulations a VUANISOHYPER_INV subroutine was implemented, and axisymmetric 4-nodes elements with reduced integration (CAX4R) were used. Besides, a damping coefficient ($\alpha = 0.1$) was used to avoid unrealistic dynamic oscillations. All the tissues were assumed to have a density close to water ($\rho = 1,225 \text{ kg/m}^3$).

**Definition of the Simulation: LS-DYNA**

Fluid structure simulations (FSI) of the air-puff were performed using the commercial finite element solver LS-DYNA 971 Release 7.0. The same structural mesh and boundary conditions as for the simulations with Abaqus were applied. Quadrilateral axisymmetric continuum solid element with reduced integration and hourglass control were used to discretise the different structures of the eye. The Demiray SEF was implemented in a user material subroutine. The incompressible fluid solver, ICFD, from LS-DYNA was used. In addition, due to the large differences in mass density between the air and the eye (three orders of magnitude), a weak coupling for the FSI was considered.

The fluid mesh (air side) was meshed with triangular elements using an adaptive mesh algorithm implemented within ICFD that automatically refine the domain in order to maintain the accuracy of the solution. For the tissues, a density of 1,225 kg/m$^3$ and a viscosity of $1.81 \times 10^{-5} \text{ kg/(m.s)}$ have been assumed for the simulations. The aqueous and vitreous humors present in the anterior and posterior chambers were modelled using Lagrangian elements exhibiting non-deviatoric stress-strain response i.e., $\sigma = P1$, with the hydrostatic pressure described by a Mie-Grüneisen equation of state of the form,$^{27}$

$$P = \frac{\rho_0 C^2 \mu [1 + (1 - \gamma_0/2)\mu]}{[1 + (S_1 - 1)\mu - S_2 \frac{\mu^2}{\mu + 1} - S_3 \frac{\mu^3}{(\mu + 1)^2}]^2} + \gamma_0 E, \quad (6.4)$$

where $P$ is the hydrostatic pressure, $\rho_0$ is the initial density of water, $\rho = 1000 \text{ kg/m}^3$, $C$ is the speed of sound in water, $C = 1520 \text{ m/s}$, $\gamma_0 = 0.35$ is the Grüneisen gamma, and $S_1 = 1.92$, $S_2 = -0.096$, $S_3 = 0.0$, and $\alpha = 0.0$ are dimensionless parameters. The anterior and posterior chambers were meshed with 370 and 1044 quadrilateral elements respectively. Finally, a damping coefficient ($\alpha = 0.1$) was used to avoid unrealistic dynamic oscillations.

$^{27}$Seetamsetti 2012
Regarding the boundary conditions of the fluid, the pipe through which the air is exerted in a NCT is considered as the fluid inlet to the system (red in Fig.6.2.d). The flow is assumed fully developed at the exit of the NCT, and the distance between the outlet of the pipe and the corneal apex was set at approximately 11 mm. Non-slip boundary conditions were set at the pipe walls (black in Fig.6.2.d). The air pulse was applied as a velocity ramp in the fluid inlet, with a peak velocity of 120 m/s (i.e. following the same time pattern described previously). The size of the fluid mesh was 10 times larger than the characteristic dimension of the eye model (i.e. the diameter of the eyeball) so as to minimise the effect of the boundary conditions on the flow over the cornea. The geometric boundaries of the air media (blue in Fig.6.2.d), are assumed as zero pressure outflow conditions. Finally, the interaction between the solid and the air occurring at the external corneal surface (black in Fig.6.2.d) is modelled following a weak coupling approach obeying to the large differences in material density between the air and the eye, as mentioned above.

**Simulation of CorVis ST**

As theoretical application exercise, the simulation of the CorVis ST device is carried out. The boundary conditions and models are exactly the same with a different temporal evolution of the air pulse. Now, instead of assuming a linear temporal evolution over the time step, a real distribution provided by OCULUS, and used in former studies, is applied. The aim of this simulation is to check if the dynamic variables obtained with different simulation strategies are within the order of magnitude of the experimental ranges reported. As only information about the maximum apical displacement in porcine corneas has been reported, we compare the rest of variables (e.g., applanation or velocity) with respect to those clinical results reported in humans. In this vein, we assume that porcine and human eyeballs should behave similarly as a whole system, as we both present similar anatomical macroscopic features and pressures. Additionally, and despite we are not simulating the ORA device, the difference in pressure between the first and second applanation (i.e. akin to the Corneal Hysteresis) is studied to discern whether it can be recovered from pure dynamical simulations or, by the contrary, the inclusion of viscoelastic properties of the corneal tissue is required. All the post-processing was carried out using the Python interface provided by Abaqus, and Matlab (MathWorks, Apple Hill, Natick, USA).

### 6.3 Results and Discussion

The results are analyzed gradually, excluding those mechanical models with the worst performance at the beginning, and keeping the most realistic combinations.
First, the maximum deformation amplitude (DA) for all the numerical tests is analyzed so as to establish an initial classification in terms of one of the most important biomarkers reported in NCTs. Second, the corneal profile at different times (t = 0, 7.5, 15 ms) is compared between 4 different numerical tests: quasi-static vs. dynamic simulations (Test 1 in Figure 6.3), IOP as uniform pressure (DSLOAD) vs. IOP as Fluid Cavity (Test 2 in Figure 6.3), Internal Structures vs. No Internal Structures (Test 3 in Figure 6.3), and Fluid Structure Interaccion simulations vs. Dynamic Mechanical simulations (Test 4 in Figure 6.3). Third, an analysis of the energies involved in the simulation is carried out to discern whether the inertial effects are important or not, and therefore if it is justified the use of dynamic simulations. Finally, a simulation of the CorVis NCT is analyzed for both the mechanical gold standard and the FSI simulations.

Impact of the Boundary Conditions in the Corneal Kinematics

First, one of the most important biomarkers reported by commercial tonometers (i.e. the maximum deformation amplitude, DA) is analyzed. All comparisons are performed with respect to the mechanical gold standard (case 6 in Figure 6.3). When comparing the DA of the pure mechanical simulations, and assuming the internal fluids as a distributed uniform pressure (DSLOAD) over the surface, the differences reaches up to a 170% (in particular case 1 vs. case 6, see in Table 6.1).

*Corneal mesh penetrates crystalline mesh.

The main reason is related to how the inner pressure is treated when using a fluid cavity. As the process of compression is isochoric, only an increment of pressure can guarantee the equilibrium. This increment of pressure, which can reach almost 3 times the initial IOP (see in Fig.6.5), is not included when using a uniform pressure where the IOP is kept constant during all the simulation. Then, accounting for this assumption would lead to an incorrect maximum DA. Not only that, when comparing dynamic simulations with a fluid cavity condition with internal structures or without them, an error of up to a 16% is obtained (in particular case 5 vs. case 6, see in Table 6.1). When the internal structures are stiffer, an error up to a 42% could be achieved (results not shown). Meaning that the internal structures act as a reinforcement, and should not be neglected since the overall stiffness would be lower. Hence, and solely regarding the maximum DA amplitude, we can conclude that the best mechanical strategy to simulate a NCT would imply taking into account

<table>
<thead>
<tr>
<th>Case Num.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tbody>
<tr>
<td>Max. DA (mm)</td>
<td>3.20</td>
<td>3.14*</td>
<td>2.86</td>
<td>2.82*</td>
<td>1.38</td>
<td>1.19</td>
<td>1.76</td>
<td>0.41</td>
</tr>
</tbody>
</table>

(*) Corneal mesh penetrates crystalline mesh.
the internal structures, the fluids as an hydrostatic pressure (Fluid cavity), and a dynamic explicit simulation (i.e. our mechanical gold standard simulation).

![Kinematics of the cornea](image)

**Figure 6.4: Kinematics of the cornea.** (a) **Test 1 (case 1 vs. case 3):** Deformation profile of the cornea in quasi-static vs. dynamic simulations (Abaqus, model with internal structures, and IOP as DSLOAD); (b) **Test 2 (case 3 vs. case 5):** Deformation profile of the cornea in simulations with IOP as DSLOAD vs. simulations with IOP as Fluid Cavity (Abaqus, model with internal structures, and dynamic explicit simulations); (c) **Test 3 (case 5 vs. case 6):** Deformation profile of the cornea in simulation with internal structures vs. simulation without internal structures (Abaqus, IOP as Fluid Cavity, and dynamic explicit simulations); (d) **Test 4 (case 6 vs. case 8):** Deformation profile of the cornea in simulation carried out with Abaqus (mechanical gold standard) vs. simulation carried out with LS-DYNA (real gold standard).

This conclusion is also supported by the deformation of the corneal profile at different time frames (see in Fig.6.4.a-c). All the corneal profiles match after the initial pressurization independently in the simulation, only a slight difference is achieved when no internal structures are accounted for. When a dynamic explicit simulation is used, the resulting deformation is lower, which means that the cornea is slightly stiffer than in a quasi-static simulation (Test 1, case 1 vs. case 3; see in Fig.6.4.a). This can be directly related either to the contribution of the mass opposing to the
movement, or to the material damping. As outlined before, when the humors are considered as an incompressible fluid the IOP increases in both chambers as the air pulse compresses the cornea (see dashed and solid blue lines in Fig. 6.5), resulting on a vastly different corneal deformation (Test 2, case 3 vs. case 5; see in Fig.6.4.b). Finally, when the internal structures are accounted for, the cornea presents a smaller maximum DA and less radial expansion (Test 3, case 5 vs case 6; see in Fig.6.4.c). As the internal structures are tying the eyeball at the joint between the cornea and the sclera, the cornea is less prone to rotate around. On the contrary, when the internal structures are disregarded, there exists a greater radial displacement of the scleral body (see grouping of dashed lines in the region comprised between 7-8 mm in X-coord. and 9-10 mm in Y-coord. in Fig.6.4.c) allowing the cornea to perform a greater rotation and, therefore, achieving a greater deformation amplitude.

When accounting for the FSI simulation with internal structures and the humors as water with mass, the maximum deformation amplitude is 3 times smaller (see in Table 6.1). As the mass of the humors is much higher than the mass of the rest of the system, a much higher energy is required to obtain the same displacement (for the same stiffness, pressures, and geometry). Not only that, but the spatial distribution of the pressure presents a non-negligible variation due to the corneal deformation, resulting on different deformation profiles (Test 4, case 6 vs. case 8; see in Fig. 6.5.d). Considering the humors as a uniform pressure is not adequate when simulating a NCT. The increment of intraocular pressure is consistent and similar in both simulations (i.e. mechanical gold standard – Abaqus, and real gold standard – LS-DYNA), and should not be disregarded (see in Fig. 6.5). Not only that, but the main advantage of the FSI simulation over the mechanical simulation is that the mass of the fluid is accounted for. As the mass of the humors is vastly greater than the rest of the mass of the system, it must be accounted for in a dynamic simulation.

Finally, and only regarding FSI simulations, the fluid domain (air) can be analyzed. The distribution of pressure over the time will change due to the deformation of the corneal profile, resulting in a non-negligible divergence of the pressure profile from the approximated Gaussian-shaped profile. A maximum pressure of 9 kPa is located at the center of the cornea (see red areas in Figure 6.6.a) but, more importantly, negative pressure areas are present (see in blue areas in Figure 6.6.a). Thus, outlining that the pressure profile over the cornea is complex, variable in time, and dependent on the deformation of the corneal profile. This fact is further supported by the distribution of the average speed over the cornea (see in Figure 6.6.b). There is a negligible loss in kinetic energy between the nozzle tip (where a maximum of 120 m/s is imposed) and the corneal apex. Furthermore, there is a boundary layer detachment and a re-circulation due to the abrupt change on cur-
Methods for Characterising Patient-Specific Corneal Biomechanics

Figure 6.5: Increment of Intraocular Pressure during Air-Jet. Increment of Intraocular Pressure (IOP) in anterior and posterior chambers due to the compression of the cornea during the air pulse. In Abaqus (solid lines), both chambers present a pressure increment of 2.3–2.6 times the initial IOP. In LS-DYNA (dashed lines), both chambers present a pressure increment of 1.7–2.3 times the initial IOP. Besides, both increments of pressure present a delay with respect to the peak of pressure of the air-jet (black solid line) due to the inertia of the system. Volume in both chambers remain constant during the simulation, ensuring an isochoric process.

 curvature in the transition between the cornea and the sclera. The difference between the lower speed close to the eyeball and the high speed farther away from the surface is responsible of the negative pressure (i.e. a suction of the eyeball). As a consequence, it could be suggested that, if we want to be accurate enough in terms of load transference, it is necessary to account for the turbulent simulation of the air alongside the deformation of the eyeball's surface over the time.

Figure 6.6: Simulation of the Fluid Domain in LS-DYNA (Highest Concavity Time). (Left Panel) Distribution of average pressure over the cornea. A peak of 9 kPa is achieved in the corneal center. (Right Panel) Average speed of the air-jet over the cornea. A peak of 120 m/s is obtained at the nozzle tip.
Analysis of Energy in the System

The dynamic simulation performed in Abaqus presents a ratio between the Kinetic Energy (ALLKE) and the Internal Energy (ALLIE) of the system (and of the cornea) that is lower than a 1%. Therefore, the inertia does not dominate and the simulation could be carried out as quasi-static (ratio lower than 5%). When the dynamic simulation is performed with LS-DYNA, the same trend is observed for the cornea. However, inertial effects dominate in the aqueous humor (peak of $\approx 16\%$, see blue solid line in Fig. 6.7), and the vitreous humor (peak of $\approx 1200\%$, results not shown). Hence, the mass of the humors is of great importance in a dynamic simulation and should be accounted for.

Dynamic Simulation of NCTs

The CorVis ST simulation with our mechanical gold standard simulation shows a good agreement with the experimental ranges reported (see in Table 6.2). Furthermore, the evolution of the biomarkers over time is also qualitatively in good agreement with the analogous reported (correlate Fig.6.1 and left panel in Fig.6.8). Interestingly and although we are using an average porcine model, with porcine mechanical properties and a thicker thickness, almost all the biomarkers range within the human range.$^{31}$ The applanation times are slightly out of the reported ranges, and the Corneal Hysteresis (i.e. difference of pressure between applanation times) is significantly out of the experimental ranges. Furthermore, there is a delay (0.3 ms) between the time at which the maximum peak pressure occurs, and the time at which the maximum DA is achieved (see in Table 6.2). The inertia of the system due to the mass can cause the movement to continue although the air pulse decreases.

When the simulation of the NCT is carried out with LS-DYNA and accounting for the humors as fluids (i.e. real gold standard), the results are also in good agreement with the experimental ranges reported (see in Table 6.2). Apart from an increment in the delay of the response (0.73 ms), the inclusion of the humors results in two re-
markable additional effects. First, the maximum displacement amplitude is reduced three times with respect to the mechanical gold standard for the same material stiffness. Second, the Corneal Hysteresis is also reduced three times, pointing to the humors as one important feature controlling this biomarker.

**Figure 6.8: Dynamic Explicit Simulation of CorVis ST.** (a) Abaqus simulation. Temporal evolution of biomarkers: apical displacement (red solid line), applanation length (green solid line), velocity (blue solid line), and normalized air pulse pressure (black dashed line); (b) LS-DYNA simulation. Temporal evolution of biomarkers: apical displacement (red solid line), applanation length (green solid line), velocity (blue solid line), and normalized air pulse pressure (black dashed line).

**Table 6.2: Experimental ranges [Hon and Lam, 2013, Luce, 2005] of the CorVis ST biomarkers, and numerical results of the Dynamic Explicit and the FSI simulations.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dynamic</th>
<th>FSI</th>
<th>Exp. Ranges</th>
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<tbody>
<tr>
<td>1st App. Time (ms)</td>
<td>10.4</td>
<td>9.3</td>
<td>7.40 – 8.27</td>
</tr>
<tr>
<td>1st App. Length (mm)</td>
<td>2.2</td>
<td>1.1</td>
<td>1.47 – 2.18</td>
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<tr>
<td>1st App. V (mm/ms)</td>
<td>-0.144</td>
<td>-0.201</td>
<td>-0.15 to -0.09</td>
</tr>
<tr>
<td>1st App. Pressure (kPa)</td>
<td>5.6</td>
<td>4.538</td>
<td>-</td>
</tr>
<tr>
<td>Peak Pressure (kPa)</td>
<td>9.0</td>
<td>9.0</td>
<td>-</td>
</tr>
<tr>
<td>Peak Time (ms)</td>
<td>15.500</td>
<td>15.500</td>
<td>-</td>
</tr>
<tr>
<td>Delay (ms)</td>
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<td>0.73</td>
<td>-</td>
</tr>
<tr>
<td>Max. DA V (mm/ms)</td>
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<td>0.05</td>
<td>-</td>
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<td>Max. DA Press. (kPa)</td>
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<td>8.91</td>
<td>-</td>
</tr>
<tr>
<td>Max. DA (mm)</td>
<td>-1.19</td>
<td>-0.41</td>
<td>0.92 – 1.36</td>
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<tr>
<td>2nd App. Time (ms)</td>
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<td>20.0</td>
<td>22.05 – 23.13</td>
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<td>2nd App. Length (mm)</td>
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<td>0.25 – 0.44</td>
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<td>2nd App. Press. (kPa)</td>
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<td>-</td>
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<tr>
<td>CH (mmHg)</td>
<td>22.5</td>
<td>6.2</td>
<td>7.9 – 10.7</td>
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<td>Max. IOP ant (kPa)</td>
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<td>4.6</td>
<td>-</td>
</tr>
<tr>
<td>Max. IOP post (kPa)</td>
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<td>-</td>
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<tr>
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<td>319.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vol. post. (mm³)</td>
<td>2576.1</td>
<td>-</td>
<td>-</td>
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6.4 Conclusions

To the best of our knowledge, it is the first time that a complete fluid-structure interaction simulation of a Non-Contact Tonometry including the air and the humors as fluid is carried out. Differences between mechanical and coupled simulations have been studied to discern whether they are interchangeable, or not. First, we have outlined that the hypothesis of simulating the internal fluid as a uniform pressure is not valid when a compression load over the cornea is considered. Since the eyeball acts as a pressurized vessel, an isochoric compression must result in an increment of the internal pressure. When considering the humors as a fluid, the IOP can increase 2–3 times the initial IOP (depending on the stiffness of the remaining elements). Second, the internal structures (lens and muscles) are mostly in equilibrium (i.e. negligible vertical displacement during the loading). However, they cannot be disregarded as they are acting as a horizontal restraint for the sclera. This passive effect (only acts in traction) modifies the kinematic of the system, avoiding a higher radial expansion than expected in those models without them. Although the impact is small, they should be accounted for when simulating accurately dynamic variables related to the deformation of the corneal profile (e.g. applanation lengths or times). In this line, we realized that a proper definition of the stiffness of the internal structures and the sclera is essential since they have an important impact on the oscillations of the system, the radial expansion of the eyeball, and the increment of pressure in the chambers (results not shown). Third, although dynamic simulations did not seem to play a major role when using a pure mechanical simulation in Abaqus, it was mainly related with the absence of the mass of the humors. When including the effect of the mass of the humors (LS-DYNA), dynamic simulations become relevant and unavoidable.

In summary, although mechanical simulations in Abaqus could incorporate a better boundary condition for the inner fluids (Fluid Cavity), still this approach does not take into account the mass of the fluid properly. Although adding a lumped mass to the back surface of the cornea has been used to circumvent this problem,\textsuperscript{32} this approach is highly dependent in the patient and the volume of the cameras and does not present a realistic boundary condition. Furthermore, considering the spatial distribution of the air-jet over the cornea as a constant bell-shaped uniform pressure overestimates the transmitted forces, and the applied area. Since the cornea modifies its shape during the experiment, it is not possible to know \textit{a priori} how the spatial distribution of pressure will be on each patient. Eventually, and due to all the aforementioned reasons, NCTs require of FSI simulations for a realistic set of boundary conditions (humors, and air-jet). Neglecting this fact when performing a material optimization could lead to overestimate the stiffness of the corneal tissue. This fact is outlined in our study when comparing the FSI and the

\textsuperscript{32} Sinha Roy et al. 2015, Simonini and Pandolfi 2016, Simonini et al. 2016
mechanical gold standard simulations with the same material properties, resulting in a vastly different displacement.

This study is not exempt of limitations. An average geometry of a pig cornea in 2D axisymmetric model is used, neglecting the use of an anisotropic hyperelastic model. Besides, the surrounding boundary conditions have been disregarded (e.g. fat tissue, extraorbital muscles, or optical nerve). Currently, we are working on extending the simulations to cope with 3D patient-specific human corneas, including anisotropy, pathologies, and external structures. Not only that, but also the viscoelastic behavior of the cornea has not been taken into account since the test is performed at high speed.\textsuperscript{33} Although we are working on incorporating viscoelastic effects to our models, we suggest in the present study that some corneal biomarkers such as the Corneal Hysteresis seems to have a strong correlation with the internal humors, and not only with the viscoelasticity of the system. Future steps will try to discern the real effect of viscoelasticity in NCTs simulations. Independently to these present limitations, conclusions regarding the modeling and simulation of NCTs remain valid, since all the models accounted for the same material properties and boundary conditions (with exemption to those related intrinsically with the simulation, such as the air-jet).

When models were applied to reproduce a CorVis NCT, results were in good agreement with the experimental results. Dynamic variables such as applanation lengths and times, or velocities were in the range of the experimental ranges. As we optimized the material parameters for the mechanical model in Abaqus, the maximum deformation amplitude was in the experimental range. On the contrary, using the material properties optimized with the mechanical model led to a lower maximum deformation amplitude. If the material parameters would be optimized using the FSI simulation, the maximum deformation amplitude of the mechanical model would result higher and out of the experimental range. Finally, when analyzing the Corneal Hysteresis (CH), our results suggest that the humors are playing a non-negligible role. The CH of the mechanical simulation ($\approx 21$ mmHg) was out of the experimental range, whereas the CH of the FSI simulation ($\approx 6$ mmHg) was three times lower and close to the experimental range. As our simulations are based in porcine corneas and the reported experiments belong to humans, the quantitative proximity of results could suggest that the inertia and pressure dominate over the morphology, or the stiffness of the tissues. Altogether, these results also outline that the mechanical response of the cornea during a tonometry presents an interplay between IOP, geometry, and material. Hence, results provided by these devices should be handled with care since they are highly biased by the effect of the internal humors, and not only by the corneal stiffness.\textsuperscript{34}

As main conclusion, if a NCT needs to be accurately simulated, we point out to the necessity of using FSI simulations, including the internal structures, and modeling


\textsuperscript{34} Ariza-Gracia et al. 2015, 2016b,a
the humors as pressurized fluids with mass. Otherwise, the application of inverse methods to retrieve the mechanical properties of the cornea can overestimate the stiffness of the tissue by including the increment of IOP in the chambers, or an untrustworthy distribution of pressure over the cornea.
Focus on the journey, not the destination. Joy is found not in finishing an activity but in doing it.

Greg Anderson

This chapter contains the main conclusions of the current work, and research lines that are currently opened and constitute the main future lines of a post-doctoral career.

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7.1 Main Conclusions and Original Contributions

Several aspects of the patient-specific geometrical and mechanical characterization of the cornea have been considered in this thesis. The main remarks are listed below,

- The mechanical response of the cornea during a non-contact tonometry (NCT) is the contribution of different factors: geometry (thickness and curvature), material stiffness of the corneal tissue, and intraocular pressure (IOP). The corneal displacement has a linear inverse relation with the IOP, and a cubic inverse relation with the thickness (due to the corneal bending). As a consequence, the right combination of these factors can result in the same corneal displacement, e.g. for the same material stiffness, a thin cornea with a high IOP could behave as a thick cornea with a low IOP (see in Chapters 2, 3, and 4).

- A novel non-supervised computational methodology has been proposed to build numerical patient-specific geometric models of the cornea using data provided by commercial topographers. This methodology is applicable to any topology, and amenable for implementation in any commercial device (see in Chapter 3).

- A zero-pressure (free-stress configuration) algorithm with a consistent mapping of the fibers from the spatial (Eulerian) to the material (Lagrangian) configuration has been proposed for the first time. In addition, the algorithm preserves the tissue volume globally. Furthermore, not accounting for the free-stress configuration of the eyeball can lead to a more compliant response of the corneal tissue and, thus, errors of approximately a 15% in the prediction of the corneal displacement (see in Chapter 3).

- A predictor of the patient-specific material properties of the cornea has been proposed. Different mathematical strategies have been applied to determine the patient-specific material properties: surface response, machine learning (SVM and MLP), and K-nn methods (K nearest neighbors). The entire methodology developed within the POPCORN project framework (i.e. patient-specific geometric reconstruction, patient-specific material prediction, and estimation of the maximum corneal displacement due to a non-contact tonometry) has been applied to a priori unknown patients (i.e. not contained in the original dataset), predicting the actual patient’s corneal displacement with an error of less than a 5%. However, a classification between healthy and pathological patients cannot be based solely on terms of the mechanical properties of the corneal tissue. This could be related to the macroscopic quasi-static analysis of the mechanical response based only in three biomarkers (i.e. displacement, IOP, and thickness), and without accounting for microstructural features. Furthermore,
the clinical ranges of deformation amplitude for healthy and pathological cases partly overlap, resulting in a too subtle mechanical difference between populations (although statistically significant). Including dynamic variables which are more sensitive to local instabilities could certainly help to increase this classification threshold. Interestingly, the minimum corneal thickness along with the maximum principal stretch of the corneal tissue have shown a promising ability in differentiating populations (see in Chapter 4).

- Under physiological conditions, the eyeball is subjected to the IOP and, then, the cornea is in "membrane" tension. On the contrary, during a NCT test, the cornea is forced to bend. Thus, posterior stroma works in tension, whereas anterior stroma works in compression. Implying that fibers embedded in the anterior stroma do not collaborate to load bearing as they are passive structural elements (i.e. only activated under traction). As a result, NCTs neither characterize the physiological state of the cornea, nor the total contribution of the fibers. To have a more complete characterization of the corneal tissue, only one bending test (NCT) could not be sufficient. Then, our suggestion is to include additional experiments that allow characterizing the "membrane" tensile state of the cornea in conjunction with clinical NCT tests to better assess on the mechanical behavior of the cornea (see in Chapters 2, 3, and 4).

- To the best of our knowledge, we propose the first numerical-experimental methodology to characterize the inflation and bending responses of the cornea simultaneously. This methodology should help to restrict the space of search of the material parameters, avoiding an ill-posed optimization. To validate the methodology, a patient-specific Astigmatic Keratotomy surgery was reproduced relying only on the optimized material properties, the patient-specific geometry, and the intraocular pressure measured. Besides, and although average models can be useful when solely optimizing mechanical properties, opto-mechanical simulations require of patient-specific geometries. To perform a proper simulation of the eye's optics, an in-house ray tracing software has been developed from scratch and validated using commercial software (OSLO). Small surface perturbations (in the order of microns) can lead to a great optical errors (in the order of diopters). Besides, topographical data provided by commercial topographers must be handled with care. To compare numerical and experimental models is compulsory to use the same optical metric. Finally, viscoelastic effects should also be accounted for when simulating surgeries. Since the patient's follow-up is not performed instantaneously, the corneal shape will slightly change due to the tissue relaxation over time (see in Chapter 5).

- To the best of our knowledge, we have carried out the first fluid-structure interaction simulation of a non-contact tonometry, including the air-jet and the humors
Outcomes and Future Lines

as fluid. The main conclusion that can be extracted is that to accurately simulate NCTs, it would be advisable to account for FSI simulations. The dynamic effects and the mass of the system are non-negligible and, therefore, must be taken into account. We based our suggestion in two main aspects. First, the pressure distribution over the cornea changes as the cornea deforms. Since the air flow over the surface of the cornea is highly dependent on the patient-specific geometry and the deformation profile over time, the pressure transferred to the cornea cannot be accounted for beforehand. Second, the humors should be simulated as incompressible fluids accounting for their masses, and being able to increment their internal pressure due to an isochoric compression. During a NCT, the eyeball experiences compression and, as a consequence, the intraocular pressure can increase 2–3 times its initial value. Besides, their masses (inertia) mainly regulate the overall dynamic response of the system, having a great impact on corneal biomarkers (e.g. the Corneal Hysteresis). Disregarding these advanced simulations would lead to overestimate the material parameters of the corneal tissue obtained by means of inverse optimization methods. Finally, our results support that the use of these devices in clinical practice should be handled with care as they are highly influenced by other factors (pressure, inertia, and geometry). Clinical biomarkers provided by NCTs do not utterly and solely depend on the stiffness of the corneal tissue (see in Chapter 6).

7.2 Scientific Publications (Journal Citation Reports)

A total of 6 (1 under preparation) journals and 1 correspondence letter contain the contribution of the present thesis,


7.3 Patent

Sistema de caracterización 3D de la respuesta mecánica del tejido de la córnea y procedimiento de medida con dicho sistema. Request Nº P201431731 (Accepted) Applicant: Alicante Oftalmológica S.L. Inventors: D. P. Piñero, N. Alcon, Á. Tolosa, M. Á. Ariza-Gracia, J. F. Rodríguez, B. Calvo

7.4 Awards

Outcomes and Future Lines

2. Mobility scholarship Fundación Ibercaja-CAI. Five months of funding to be research fellow at Politecnico di Milano.

3. ESKAS Excellence Scholarship awarded by the Swiss Government. Rate of success of ≈ 15%


7.5 Conferences

The present work has been presented in a total of 21 conferences (17 international and 4 national), from which 13 were oral presentations (1 invited presentation), and 8 posters. The 10 more relevant conferences are,


Methods for Characterising Patient-Specific Corneal Biomechanics


7.6 Other Relevant Publications


7.7 Future Lines

Among many, some of the more immediate and accessible research lines that the present thesis has opened are,

1. Remodeling tissue algorithm for determination of ectatic evolution. The aim of this research line is to develop a numerical algorithm for the qualitative prediction of ectatic diseases, such as Keratoconus. An elastoplastic formulation will be used to describe non-reversible changes due to the disruption of the collagen network of fibers. Eventually, this approach could be helpful to study the effectiveness of intracorneal segment rings (ICRS) as stabilization elements in ectatic disorders.

2. Cross-linking (CXL) simulations and collagen microstructure. Additionally to ICRS, CXL treatments are used to stabilized ectatic disorders. A better understanding, along with a simulation capability should help the ophthalmologist to decide the best surgical plan and follow-up treatment.

3. Viscoelastic modeling of corneal tissue. As we observed during the maturing of the research carried out in the present thesis, viscoelastic effects should not be disregarded when performing follow-up studies of surgeries. Although in NCTs the application of the load is almost instantaneous and viscoelastic effects can be disregarded, when studying the effect of surgeries the relaxation effect of the tissue in time should be accounted for.

4. 3-Dimensional fluid-structure simulations of NCTs with real boundary conditions. The next natural step of Chapter 6 is to extend our 2D FSI simulations to 3 dimensions, allowing to include the distribution of collagen fibers. Furthermore, we are in active collaboration with the Institute for Surgical Technology and Biomechanics (ISTB, Universität Bern) to include a real CT-segmented model of the human skull so as to take into account the set of realistic boundary conditions present during the clinical test.

5. Re-optimize the corneal properties including the acquired know-how. Also as natural evolution of the present work, a re-optimization of the mechanical properties of the cornea should be addressed accounting for more realistic boundary conditions, and more advanced simulation tools.

6. Framework to simulate laser surgeries. Currently, I am working in collaboration with the Institute for Surgical Technology and Biomechanics (ISTB, Universität Bern) to develop a computational framework that allows performing non-supervised opto-mechanical patient-specific simulations of wavefront-guided laser surgeries.
A

Sumario y Conclusiones en Español

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A.1 Sumario

Esta tesis aborda la reconstrucción un modelo numérico paciente-específico de la córnea humana, utilizando su geometría y sus propiedades mecánicas paciente específico. Se proponen diversos métodos para reconstruir automáticamente la geometría paciente-específico de la córnea, así como diferentes protocolos para determinar las propiedades paciente-específico del tejido corneal bajo diversas condiciones de carga. La salud ocular se ha vuelto muy importante durante la última década, extendiéndose gracias al incremento de seguridad de los procesos quirúrgicos y la reducción de costes. Sin embargo, supra- (o infra-) correcciones post-quirúrgicas todavía causan cierto grado de deficiencias visuales, insatisfacción en el paciente, e incremento de costes debido a segundas cirugías. Además, la preocupación sobre el origen biomecánico de ciertas patologías, como el queratocono, ha impulsado la búsqueda de una mejor definición de las propiedades mecánicas de los tejidos oculares. En este sentido, los tonómetros de no-contacto (NCTs), o aparatos de soplo de aire, se han convertido en un referente en Oftalmología a la hora de realizar asesoramiento intraquirúrgico, o para obtener más información sobre las propiedades mecánicas del tejido corneal patológico y sano.

A lo largo de esta tesis, nuestra contribución al campo de la Biomecánica Corneal se presenta en base a distintos hitos. Primero, se ha desarrollado un estudio teórico in silico para comprender mejor los fundamentos físicos de los tonómetros de no-contacto, el papel de las distintas características oculares (presión intraocular, rigidez de material, y geometría), y lo que realmente se mide con estos aparatos. Segundo, se ha desarrollado una nueva metodología automática que permite reconstruir la geometría paciente-específico allí donde se ha medido (usando topógrafos comerciales), y que permite realizar la simulación de un test genérico de soplo de aire. Tercero, se han propuesto diversas técnicas matemáticas para predecir las propiedades paciente-específico del tejido corneal a partir de biomarcadores clínicos (desplazamiento máximo en una tonometría de no-contacto, la presión intraocular, y la geometría), demostrando la capacidad de los métodos numéricos en la ayuda para la planificación de diferentes tratamientos quirúrgicos. Cuarto, se ha propuesto un nuevo protocolo numeric-experimental para determinar las propiedades del tejido corneal usando tests de inflado e indentación. En este línea, se trata de evitar una optimización mal condicionada al minimizar ambos estados tensionales simultáneamente. Quinto, usando la información paciente-específico obtenida mediante el protocolo mencionado anteriormente, se han realizado simulaciones paciente-específico de cirugías de arcuatas (Queratotomía Astigmática) en un modelo animal (Conejo de Nueva Zelanda). Adicionalmente, se ha desarrollado un algoritmo propio de trazado de rayos, el cual se ha validado con software comercial (OSLO), de forma que se
asegure la equivalencia de métricas ópticas cuando se comparan datos numéri-
cos y experimentales. De esta forma, se asegura una validación y un proceso de
optimización consistentes. Sexto, puesto que las tonometrías de no-contacto pre-
sentan un acoplamiento entre fluidos (aire, humores) y estructura (globo ocular),
se han aplicado modelos de interacción fluido-estructura (FSI) para mejorar las
simulaciones incluyendo transferencias de carga y condiciones de contorno más
realistas. Adicionalmente, se ha estudiado si las simulaciones FSI son necesarias
o bajo qué hipótesis pueden ser sustituidas por simulaciones dinámicas puramente
estructurales sin pérdida de generalidad.

**Palabras clave:** Biomecánica corneal, Tonometro de no-contacto, geometría, ma-
terial, óptica, optimización, elementos finitos, interacción fluido-estructura, paciente-
específico, trazado de rayos.

### A.2 Conclusiones Principales y Contribuciones Originales

Diferentes aspectos de la caracterización mecánica del tejido corneal se han con-
siderado en esta tesis. Los principales logros se detallan a continuación,

- La respuesta mecánica de la córnea durante una tonometría de no-contacto
  (NCT) es la combinación de distintos factores: geometría (espesor y curvatura),
  rigidez de material, y presión intraocular (IOP) del ojo. El desplazamiento corneal
tiene una relación lineal inversa con la IOP y una relación cúbica inversa con el
  espesor (debido a la flexión de la córnea). Como resultado, la adecuada com-
binación de estos factores puede resultar en el mismo desplazamiento corneal,
  por ejemplo, para la misma rigidez de material, una córnea delgada con una
  IOP elevada podría comportarse de la misma forma que una córnea gruesa con
  una IOP baja (ver Capítulos 2, 3, y 4).

- Se ha propuesto una nueva metodología computacional no-supervisada para
  construir modelos geométricos paciente-específico de la córnea utilizando los
  datos proporcionados por topógrafos corneales comerciales. Esta metodología
  se puede aplicar a cualquier topología, y se puede implementar en cualquier
  aparato comercial (ver Capítulo 3).

- Se ha propuesto un algoritmo de cero-presión (configuración sin carga) con un
  mapeado consistente de las fibras desde la configuración espacial (Euleriana)
a la configuración material (Lagrangiana). El algoritmo preserva el volumen del
tejido globalmente. Además, no tener en cuenta esta configuración de refer-
encia sin carga puede llevar a una respuesta más flexible del tejido corneal y,
  por tanto, a errores de aproximadamente el 15% en la predicción del desplaza-
miento corneal (ver Capítulo 3).
• Se ha propuesto un predictor de las propiedades paciente-específico del tejido corneal. Se han aplicado diferentes estrategias matemáticas para predecir las propiedades mecánicas: superficies de respuesta, machine learning (SVM y MLP), y métodos K-nn (vecino más cercano). La metodología completa desarrollada en el marco del proyecto europeo POPCORN (es decir, la reconstrucción geométrica paciente-específico, la predicción de material paciente-específico, y la estimación del desplazamiento máximo del ápex corneal durante una tonometría de no-contacto) se ha aplicado a pacientes desconocidos a priori (no incluidos en la base de datos o entrenamiento previo), prediciendo el desplazamiento real del paciente con errores inferiores al 5%. Sin embargo, no se puede realizar una clasificación entre ojos sanos y patológicos basada únicamente las propiedades de material. Esto puede estar relacionado con el análisis macroscópico y quasi-estático de la respuesta mecánica del tejido corneal utilizando solo 3 biomarcadores (desplazamiento, IOP, y espesor). Puesto que los rangos clínicos de desplazamiento para ojos sanos y patológicos se solapan parcialmente, las diferencias mecánicas entre ambas poblaciones son muy sutiles (aunque estadísticamente significativas). La inclusión de variables dinámicas con mayor sensibilidad a inestabilidades locales podría ayudar a incrementar el umbral de clasificación. Interesantemente, el espesor mínimo corneal junto con la deformación máxima principal del tejido corneal han demostrado ser prometedores a la hora de diferenciar poblaciones sanas y con queratocono (ver Capítulo 4).

• Bajo condiciones fisiológicas, el globo ocular está sometido a la presión intraocular y, por tanto, el estado tensional de la córnea es de membrana. Al contrario, durante una tonometría de no-contacto, se fuerza la flexión de la córnea. Por lo tanto, el estroma de la parte posterior trabaja a tracción, mientras que el estroma de la parte anterior trabaja a compresión. Esto implica que las fibras de colágeno del estroma anterior no soportan carga puesto que son elementos estructurales pasivos (es decir, sólo activados a tracción). Como resultado, las tonometrías de no-contacto no caracterizan un estado fisiológico de la córnea, ni la contribución total de las fibras. Para realizar una caracterización más completa del tejido corneal, solamente un ensayo de flexión (NCT) podría no ser suficiente. Por lo tanto, nuestra sugerencia consiste en incluir experimentos adicionales que permitan caracterizar el estado de tensión de membrana de la córnea junto a ensayos clínicos de flexión (NCT) para un mejor asesoramiento del comportamiento mecánico de la córnea (ver Capítulos 2, 3, y 4).

• Se ha propuesto por primera vez una metodología numérico-experimental que caracteriza las respuesta de inflado y flexión de la córnea simultáneamente. Esta metodología debería ayudar a restringir el espacio de búsqueda de los parámetros de material, evitando una optimización mal condicionada. Para vali-
dar la metodología, se han simulado numéricamente cirugías de arcuatas (Que- 
ratotomía Astigmática) paciente-específico utilizando únicamente las propieda-
des de material obtenidas con el protocolo propuesto, la geometría paciente-es-
pecífico, y las medidas de presión intraocular. Aunque los modelos geométricos
promedio pueden ser útiles cuando se caracterizan las propiedades mecánicas,
as las simulaciones opto-mecánicas requieren el uso de geometrías acien-
te-específico. Para realizar una correcta simulación de la óptica del ojo, se ha
desarrollado y validado (OSLO) un software propio de trazado de rayos. Una
pequeña diferencia en la superficie corneal (del orden de micras) puede llevar a
un gran error óptico (en el orden de las dioptrías). Además, los datos topográfi-
cos de los aparatos comerciales se deben utilizar con cuidado. Para comparar
los modelos numéricos y experimentales es obligatorio utilizar la misma métrica
óptica. Finalmente, también se deberían tener en cuenta los efectos viscoelásti-
ticos cuando se simulan las cirugías. Puesto que el seguimiento del paciente
no se realiza de forma instantánea, la córnea cambiará ligeramente su forma
debido a la relajación del tejido (ver Capítulo 5).

• Se ha realizado la primera simulación fluido-estructura (FSI) completa de una
tonometría de no-contacto, incluyendo el chorro de aire y los humores como
fluidos. La principal conclusión que se puede extraer es que, para simular de
forma precisa una tonometría de no-contacto, es aconsejable utilizar simula-
ciones FSI. Los efectos dinámicos y la masa del sistema no son despreciables
y, por lo tanto, se deben tener en cuenta. Basamos nuestra sugerencia en dos
aspectos fundamentales. Primero, la distribución de presión sobre la córnea
cambia conforme la córnea se deforma. Por lo tanto, la distribución de pre-
sión sobre la córnea no se puede predecir de antemano puesto que el flujo
de aire sobre la superficie corneal es altamente dependiente de la geometría
paciente-específico y en el perfil de deformación a lo largo del tiempo. Se-
gundo, los humores se deberían simular como un fluido incompresible teniendo
en cuenta las masas y siendo capaces de incrementar la presión interna du-
rante un proceso de compresión isócosa. En una tonometría de no-contacto,
el globo ocular experimenta una compresión y, como consecuencia, la presión
intraocular incrementa entre 2 y 3 veces su valor inicial. Además, las masas de
los humores (inercia) son las que regulan la respuesta dinámica global del sis-
tema, teniendo un gran impacto en los biomarcadores corneales (por ejemplo,
la histéresis corneal). Evitar el uso de estas simulaciones avanzadas podría
llevar a sobreestimar las propiedades de material del tejido corneal obtenidos
mediante optimización inversa. Finalmente, nuestros resultados apoyan que el
uso de estos aparatos en la práctica clínica debería ser realizado con cuidado
puesto que están altamente influenciados por otros factores (presión, inercia
y geometría). Los biomarcadores corneales clínicos provistos por los tonóme-
tros de no-contacto no dependen completa y únicamente en la rigidez del tejido corneal (ver Capítulo 6).

Todo el trabajo se ha recogido en varias publicaciones en revistas con alto factor de impacto (ver 7.2), una patente (ver 7.3), varios premios y menciones especiales (ver 7.4), y diversas conferencias internacionales (ver 7.5).

A.3 Lineas Futuras

Entre muchas, algunas de las líneas de investigación más inmediatas y accesibles que he abierto con esta tesis son,

1. Formular algoritmos de remodelado de tejidos para la determinacion de la evolución ectásica. El objetivo de esta línea de investigación es desarrollar un algoritmo numérico para la predicción cualitativa de enfermedades ectásicas, como el Queratocono. Una formulación elastoplástica se utilizará para describir cambios no-reversibles debido a la disrupción de la red de fibras de colágeno. Finalmente, esta propuesta podría ser útil para estudiar la efectividad de la implantación de anillos intracorneales (ICRS) como elemento de estabilización de estos desórdenes.

2. Simulaciones de cross-linking (CXL) y microestructura del colágeno. Adicionalmente a los ICRS, los tratamientos de CXL se utilizan para la estabilización de desórdenes ectásticos. Un mejor conocimiento de estos elementos unido a capacidades de simulación podrían ayudar a los oftalmólogos a decidir cual es el mejor plan quirúrgico y de tratamiento de seguimiento.

3. Modelado viscoelástico del tejido corneal. Durante la maduración de la investigación realizada se ha observado que los efectos viscoelásticos no deberían despreciarse cuando se realizan estudios de seguimiento de cirugías. Aunque las tomometrías de no-contacto aplican una carga casi instantánea y los efectos viscoelásticos se pueden despreciar, cuando se estudian cirugías se deberían tener en cuenta los efectos de relajación del tejido en el tiempo.

4. Simulaciones FSI en 3D con condiciones de contorno reales. El siguiente paso natural del capítulo 6 es extender nuestros modelos FSI en 2D a 3 dimensiones, permitiendo la inclusión de las fibras de colágeno. Además, estamos en colaboración activa con el Instituto de Tecnología Quirúrgica y Biomecánica (ISTB, Universidad de Berna) para incluir modelos reales segmentados del cráneo (tomografía computerizada) para introducir condiciones de contorno más reales.

5. Re-optimización de las propiedades corneales incluyendo el conocimiento adquirido. También como evolución natural del presente trabajo, las propiedades
mecánicas de la córnea deberían re-optimizarse teniendo en cuenta condiciones de contorno más realistas y herramientas computacionales más avanzadas.

6. Herramienta para la simulación de cirugías laser. Actualmente, estoy trabajando en colaboración con el ISTB para desarrollar un marco computacional que permita realizar simulaciones opto-mecánicas paciente-específico no-supervisadas de cirugías láser guiadas por wavefront.
B

Publications

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Abstract

The mechanical response of the cornea subjected to a non-contact air-jet tonometry diagnostic test represents an interplay between its geometry, the corneal material behavior and the loading. The objective is to study this interplay to better understand and interpret the results obtained with a non-contact tonometry test. A patient-specific finite element model of a healthy eye, accounting for the load free configuration, was used. The corneal tissue was modeled as an anisotropic hyperelastic material with two preferential directions. Three different sets of parameters within the human experimental range obtained from inflation tests were considered. The influence of the IOP was studied by considering four pressure levels (10–28 mmHg) whereas the influence of corneal thickness was studied by inducing a uniform variation (300–600 microns). A Computer Fluid Dynamics (CFD) air-jet simulation determined pressure loading exerted on the anterior corneal surface. The maximum apex displacement showed a linear variation with IOP for all materials examined. On the contrary, the maximum apex displacement followed a cubic relation with corneal thickness. In addition, a significant sensitivity of the apical displacement to the corneal stiffness was also obtained. Explanation to this behavior was found in the fact that the cornea experiences bending when subjected to an air-puff loading, causing the anterior surface to work in compression whereas the posterior surface works in tension. Hence, collagen fibers located at the anterior surface do not contribute to load bearing. Non-contact tonometry devices give useful information that could be misleading since the corneal deformation is the result of the interaction between the mechanical properties, IOP, and geometry. Therefore, a non-contact tonometry test is not sufficient to evaluate their individual contribution and a complete in-vivo characterization would require more than one test to independently determine the membrane and bending corneal behavior.

Automatized Patient-Specific Methodology for Numerical Determination of Biomechanical Corneal Response

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Abstract—This work presents a novel methodology for building a three-dimensional patient-specific eyeball model suitable for performing a fully automatic finite element (FE) analysis of the corneal biomechanics. The reconstruction algorithm fits and smooths the patient’s corneal surfaces obtained in clinic with corneal topographers and creates an FE mesh for the simulation. The patient’s corneal elevation and pachymetry data is kept where available, to account for all corneal geometric features (central corneal thickness-CCT and curvature). Subsequently, an iterative free-stress algorithm including a fiber’s pull-back is applied to incorporate the pre-stress field to the model. A convergence analysis of the mesh and a sensitivity analysis of the parameters involved in the numerical response is also addressed to determine the most influential features of the FE model. As a final step, the methodology is applied on the simulation of a general non-commercial non-contact tonometry diagnostic test over a large set of 130 patients—53 healthy, 33 keratoconic (KTC) and 41 post-LASIK surgery eyes. Results show the influence of the CCT, intraocular pressure (IOP) and the external forces acting upon it such as an external pressure. An imbalance between these parameters, e.g. an increment of IOP (glaucoma), a decrement of the corneal thickness induced by refractive surgery or by a corneal material weakening due to a disruption of collagen fibers (keratoconus), can produce ocular pathologies (ectasias) which seriously affect patient’s sight. Consequently, it is important to understand how ocular factors such as IOP, geometry and corneal material are related to pathologies in order to improve treatments. The first step in this direction consists of the correct measurement of the IOP and corneal topography. To date, the IOP is measured by either contact tonometers, e.g. Goldmann Applanation Tonometry (e.g. Goldmann Applanation Tonometry (GAT)), or non-contact tonometers, e.g. CoVit ST (Oculus Optikgeräte GmbH) or Sirius (Schwind eye-tech-solutions GmbH & Co.KG), which have reached a high level of sophistication and accuracy.

INTRODUCTION

The corneal shape is the result of the equilibrium between its mechanical stiffness (related to the corneal geometry and the intrinsic stiffness of the corneal tissue), intraocular pressure (IOP) and the external forces acting upon it such as an external pressure. An imbalance between these parameters, e.g. an increment of IOP (glaucoma), a decrement of the corneal thickness induced by refractive surgery or by a corneal material weakening due to a disruption of collagen fibers (keratoconus), can produce ocular pathologies (ectasias) which seriously affect patient’s sight. Consequently, it is important to understand how ocular factors such as IOP, geometry and corneal material are related to pathologies in order to improve treatments. The first step in this direction consists of the correct measurement of the IOP and corneal topography. To date, the IOP is measured by either contact tonometers (e.g. Goldmann Applanation Tonometry) or non-contact tonometers, e.g. CoVit ST (Oculus Optikgeräte GmbH) whereas the corneal topography is obtained with corneal topographers, e.g. Pentacam (Oculus Optikgeräte GmbH) and Sirius (Schwind eye-tech-solutions GmbH & Co.KG), which have reached a high level of sophistication and accuracy.

The availability of high resolution topographical data and the patient’s IOP have made possible to reconstruct a patient’s specific geometric model of the cornea, which makes it possible to study specific treatments and pathologies. In this regard, some patient-specific corneal models have already been reported in the literature. However, the pipeline...
A predictive tool for determining patient-specific mechanical properties of human corneal tissue

Miguel Ángel Ariza-Gracia, Santiago Redondo, David Piñero Llörenco, Begoña Calvo, José Felix Rodríguez Matas

Abstract

A computational predictive tool for assessing patient-specific corneal tissue properties is developed. This predictive tool considers as input variables the corneal central thickness (CCT), the intraocular pressure (IOP), and the maximum deformation amplitude of the corneal apex (U) when subjected to a non-contact tonometry test. The proposed methodology consists of two main steps. First, an extensive dataset is generated using Monte Carlo (MC) simulations based on finite element models with patient-specific geometric features that simulate the non-contact tonometry test. The cornea is assumed to be an anisotropic tissue to reproduce the experimentally observed mechanical behavior. A clinical database of 130 patients (53 healthy, 63 keratoconic and 14 post-LASIK surgery) is used to generate a dataset of more than 9000 cases by permuting the material properties. The second step consists of constructing predictive models for the material parameters of the constitutive model as a function of the input variables. Four different approximations are explored: quadratic response surface (QRS) approximation, multiple layer perceptron (MLP), support vector regressor (SVR), and K-nearest neighbor search. The models are validated against data from five real patients. The material properties obtained with the predicted models lead to a simulated corneal displacement that is within 10% error of the measured value in the worst case scenario of a patient with very advanced keratoconus disease. These results demonstrate the potential and soundness of the proposed methodology.

Keywords: Corneal biomechanics; Finite element modeling; Monte Carlo analysis; Patient-specific material

ABSTRACT

PURPOSE: To assess the feasibility of characterizing and following up the mechanical behavior of the corneal tissue after corneal cross-linking (CXL) by using a combined mechanical (in vivo indentation and in vitro uniaxial tensile tests) and morphological (immunohistochemistry) experimental protocol.

METHODS: CXL (3 mW/cm²; 370 nm) for 20 minutes (total dose 3.6 J/cm²) was performed on 12 New Zealand rabbits. The mechanical behavior of the cornea was characterized in small and large strain regimens using an in vivo indentation test with a laboratory device and an in vitro uniaxial tensile test, respectively. These tests and corneal immunohistochemistry were performed before (PreCXL) and on the 7th (PostCXL-7d) and 56th days (PostCXL-56d) after CXL. The intraocular pressure and corneal thickness were measured before each test.

RESULTS: For the indentation tests, significant differences were found between PreCXL and PostCXL-7d and between PostCXL-7d and PostCXL-56d, but not between PreCXL and PostCXL-56d. On average, for the small strain regimen, PostCXL-7d corneas showed the most compliant behavior, with progressive recovery of the corneal stiffness over time. For the large strain regimen, significant differences in the maximum tangential modulus between PreCXL and PostCXL-7d and between PreCXL and PostCXL-56d were observed for the uniaxial tensile tests, with no significant differences between PostCXL-7d and PostCXL-56d. Immunohistochemistry showed a lack of cells in the anterior stroma at PostCXL-7d, but at PostCXL-56d the cell density and morphology were comparable to PreCXL.

CONCLUSIONS: Indentation tests cannot characterize the changes in the corneal collagen scaffold caused by the CXL, but the uniaxial test can. However, indentation tests can assess the recovery of keratocyte density after CXL.

Why Non-contact Tonometry Tests Cannot Evaluate the Effects of Corneal Collagen Cross-linking

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Why Indentation Cannot Be Considered Exactly Equivalent to Non-contact Tonometry

We read the article by Ortillés et al. in the March 2017 issue that compared the indentation method with uniaxial extensiometry results in rabbit eyes with great interest. Unfortunately, we observed that the analyses of the results did not match the conclusions. Further, the experimental methods were incomplete and lacked sound understanding of tissue mechanics. First, the authors have considered indentation to be similar to non-contact tonometry mechanically. This is incorrect because indentation applies a concentrated force over a small area. Non-contact tonometry applies a distributed air-pressure over a significantly larger area. The deformation characteristics of the two and duration of the test are vastly different. Second, the data in Figures 3 and 4 are confusing. In Figures 3A and 3B, it is clear that post-corneal crosslinking (postCXL) 7d and 56d corneas were more compliant than the preCXL state. Figures 3C and 3D agree with the results shown in Figures 3A and 3B. For example, the force versus U curves of 7d and 56d time points were to the right of the preCXL state, with 7d being the most compliant. The same is indicated in Figure 3C, which reports the stiffness or the slope of the curves plotted in Figure 3A. When other studies have reported stiffening after CXL using indentation, it is unclear why the experimental data in this study was different.

In Figure 4A, the stress versus stretch (expressed as [1.0 ± uniaxial strain] in the direction of applied load) at different time points was presented. Here as well, the trends were the same (ie, both 7d and 56d were more compliant globally compared to preoperative time point of measurement). Third, it appears that the authors have evaluated the tangent moduli at one experimental data in this study was different. 1 It is not supported by the analyses. In fact, the proposed compressive (negative) stress versus stretch curve (Figure 6) is a physical response commonly seen with mechanical testing of polymers but not tissue. This is because collagen fibers in cornea exhibit a crimping behavior and cannot bear compressive stress. In other words, the stress versus stretch curve (Figure 6) in the compressive (negative stress) zone would generally be linear (or a straight line). We believe that the authors need to reanalyze the data carefully before suggesting any conceptual model.

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Reply
We would like to thank Drs. Sinha Roy and Shetty for their comments regarding our article. It is comforting to see that our research is appreciated by our colleagues. However, we do not fully agree with their observations and provide detailed responses in consequence.

We agree that the area of the indenter is smaller than the actual ‘soft’ area of influence associated with the air-puff, which cannot be precisely controlled during real experiments and, therefore, the loading acting on the cornea will be different in both cases. However, saying that indentation applies a concentrated load on a very small area is not entirely correct because the “smallness” of the area must be defined with respect to the surface on which the load is applied. In our case, the indentation to corneal area ratio was 1/10, which...

A numerical-experimental protocol to characterize corneal tissue with an application to predict astigmatic keratotomy surgery

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ABSTRACT

Tonometers are intended to measure the intraocular pressure (IOP) and the quality of corneal tissue. In contrast to the physiological state of the cornea, tonometers induce non-physiological bending stress. Recently, the use of a single experiment (i.e., a relaxed state of corneal mechanical properties) was suggested to be an ill-posed problem. Thus, we propose a numerical-experimental protocol that uses inflation and indentation experiments simultaneously, defining the optimization space to circumvent the ambiguity of the fitting. For the first time, both corneal behavior (i.e., limited strain (physiological) and bending (non-physiological)) are taken into account. The experimental protocol was performed using an animal model (New Zealand rabbit) cornea. The patient-specific geometry and the IOP were registered using a MOIR tonographer (CSO, Italy) and an applanation tonometer, respectively. The mechanical response was evaluated using inflation and indentation experiments. Subsequently, the optimal set of material properties is identified via an inverse finite element method. To validate this methodology, an in vivo incisional refractive surgery (astigmatic keratotomy, AK) is performed on four animals. The optical outcomes showed a good agreement between the real and simulated surgery, indicating that the proposed AK-HMC provides a reliable set of mechanical properties that enables further applications and simulations.

1. Introduction

In visual healthcare, an increasing number of efforts are being made toward proper corneal characterization to assess refractive surgeries (Studart et al., 2013), to study the effect of sectional segment rings (OCT) in keratometric stabilization (Krantz et al., 2015), to plan better surgical interventions, and to qualitatively predict the evolution of a pathology (Romero-Jiménez et al., 2010; Saunders and Harper, 2015). Commercial devices aim at discriminating the quality of corneal tissue by applying external pressure to the cornea (i.e., tonometers). Contact tonometers (e.g., Goldmann-applanation tonometry) determine the intraocular pressure (IOP) of the eye, Non-contact tonometers, or air-puff tonometers (e.g., Cornea ST-1000 Oculus), aim at determining the IOP and the quality of the corneal tissue based on the corneal deformation (Pi eros and Alió, 2014). There are important differences between them. Contact tonometers use a small plastic cylinder to indent the cornea (i.e., a displacement-driven contact test), whereas non-contact tonometers use an air jet to induce the motion of the cornea (i.e., a force-driven non-contact test). Although useful, non-contact tonometers have several associated uncertainties, such as the exact area affected by the air jet, the distance and alignment of the patient with the device, and the intrinsic geometry of the patient’s cornea. Thus, displacement-driven contact tests are more reliable since they accurately control the application and positioning of the force during the test, reducing the bias introduced in the experiments. Finally, there is generally a difference in the type of loading applied by tonometers to induce non-physiological stresses on the corneal tissue (Ariza-Gracia et al., 2015, 2016b).

In contrast to the natural membrane-like state of stress of the cornea, tonometers bend the corneal tissue. When the eyeball is physiologically loaded (i.e., biocular tension due to the IOP), see white point in...
Diurnal changes in corneal geometry, pachymetry, and intracocular pressure (IOP) in a healthy eye were recorded. The deformation response to an air puff was simulated using 3 levels of corneal stiffness. The response was dependent on IOP and pachymetry and not only on the biomechanical properties of the cornea. Similarly, the maximum variability due to the diurnal changes in pachymetry and IOP in the corneal displacement generated by the air puff was found to reach 5%. Therefore, diurnal changes in IOP and corneal thickness were able to induce some variability in the air puff-based corneal deformation response. This potential variability should be considered when the biomechanical properties of the cornea are analyzed with air-puff devices.

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In recent years, devices that measure the corneal biomechanics in clinical practice have been developed and released. All the devices are based on analysis of the corneal deformation response to an air puff. However, this deformation is influenced not only by the biomechanical properties of the cornea, but also by the intracocular pressure (IOP) and the corneal thickness. Therefore, IOP and corneal thickness should be considered when analyzing the results obtained with the devices.

Because IOP and corneal thickness vary during the day in every individual, they are expected to have a clinical relevance to measurements of the corneal biomechanical properties. Kida et al. found that corneal hysteresis (CH) measured with a dynamic bidirectional applanation device (Ocular Response Analyzer, Reichert Technologies) showed an inconsistent 24-hour variation, with no evidence of being influenced by 24-hour changes in IOP. A similar finding was reported by Shen et al. However, González-Molion et al. found that changes in CH measured with the same device correlated well with changes in IOP, suggesting that diurnal IOP variations could be related to changes in corneal biomechanics. Likewise, Lau and Pyle suggested that diurnal variations in central corneal thickness (CCT) and corneal resistance factor (CRF) measured with the dynamic bidirectional applanation device may significantly affect the tonometry measurements.

This case report shows preliminary numerical results about the interaction between pachymetric and
Advances in measuring corneal biomechanical properties

The POPCORN project has led to the development of a dynamic topographer suitable for rapid 3D mapping of the corneal surface.

**The POPCORN project**

The POPCORN project is a European project, within the Seventh Framework (Grant Agreement 606634), that has just finished, producing interesting results on the clinical characterisation of corneal biomechanics (www.popcornproject.eu). The aim of the project was to develop a device to characterise the mechanical properties of the cornea based on a plenoptic imaging system and an advanced biomechanical model that has been patented. The project has been developed by a consortium of small and medium enterprises (SMEs) and technological institutes and coordinated by Alicante Oftalmologica OFTALMAR, an ophthalmological clinic founded in 1996 within the Vithas Medimar International Hospital. The POPCORN consortium includes the SMEs Biotronics 3D from the United Kingdom, Optoelectronica 2001 from Romania and Costruzione Strumenti Oftalmici (CSO) from Italy, as well as the Applied Mechanics and Biongineering Research Group from the University of Zaragoza (Spain) and the UK Intelligent Systems Research Institute (Figure 1).

“The transparent cornea, a living tissue, is the most important component of the outer ocular layers.”

**3D mapping of the cornea with plenoptics**

The transparent cornea, a living tissue, is the most important component of the outer ocular layers. The peculiar structure of the stromal collagen lamellae provides the cornea’s specific mechanical properties. In order to understand the consequences of modification of the geometry of the first corneal surface by means of intraocular ring segments or laser refractive surgery, it is essential to predict the cornea’s biomechanical behaviour.1 The analysis of corneal biomechanics is also crucial to improve the diagnosis and management of ectatic corneal...
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C.1 Incompressible Hyperelastic Constitutive Model: Strain Energy Function and Derivatives

The strain energy function (SEF) used during the present works (C.1a) is used to describe the material behavior of the corneal stroma taking into account two different contributions. First, a Demiray SEF\(^1\) (C.1b) is used to describe the hyperelastic isotropic behavior of the ground substance (extracellular matrix) where the collagen fibres are embedded. Second, a Gasser-Holzapfel-Ogden SEF\(^2\) (C.1c) is used to describe the hyperelastic response of the collagen fibers and to provide with the anisotropic response of the corneal tissue. Both terms are combined along with a volumetric term (\(\psi_{\text{vol}}\)) (C.1e), or (C.1f), to define the mathematical corneal behavior for simulation as,

\[
\psi = \tilde{\psi}_D(\tilde{C}) + \tilde{\psi}_{\text{GOH}}(\tilde{C}) + \psi_{\text{vol}}(J)
\]

![Image](image.png)

\[
\tilde{\psi}_D(\tilde{C}) = D_1 \cdot (e^{D_2 \cdot (I_1 - 3)} - 1)
\]

\[
\tilde{\psi}_{\text{GOH}}(\tilde{C}) = \frac{k_1}{2 \cdot k_2} \cdot \sum_{a=1}^{N} \left( e^{k_2 (E_a)^2} - 1 \right)
\]

\[
E_a \overset{\text{def}}{=} \kappa \cdot (I_1 - 3) + (1 - 3\kappa) \cdot (I_4_{\alpha\alpha}) - 1
\]

\[
\psi_{\text{vol}}(J) = \frac{1}{D} \cdot \left( \frac{J_{\text{el}}^2 - 1}{2} - \ln(J_{\text{el}}) \right)
\]

or, a simpler alternative, \(\psi_{\text{vol}}(J) = \kappa_0 (J - 1)^2\)

where \(\kappa_0 = \frac{1}{D}\) is the bulk modulus, \(J_{\text{el}} = \det F\) is the elastic volume ratio, \(D_1\) and \(D_2\) are the parameters of the isotropic term (\(\tilde{\psi}_D\)), \(I_1\) is the first invariant of the modified right Cauchy-Green tensor (\(\tilde{C} = J_{\text{el}}^{-2/3} C = J_{\text{el}}^{-2/3} F^T F\)), \(F\) the deformation gradient, \(k_1\) and \(k_2\) were the parameters of the anisotropic term, \(\tilde{\psi}_{\text{GOH}}\), \(I_4 = n_a \cdot C n_a\) is the square of the stretch along the fibre direction \((n_a)\), and \(\kappa \in [0, \frac{1}{3}]\) is the dispersion parameter of the fiber along the direction. For the sake of simplicity, we will assume in this section that SEFs will be always dependent on the modified right Cauchy-Green tensor (\(\tilde{C}\)), but we will skip the cumbersome upper-bar notation (i.e. \(\tilde{I}_m = I_m\)).
The derivatives of the proposed isotropic SEF ($\psi_D$) are,

\[
\psi_D^1 = \frac{\partial \psi_D}{\partial I_1} = D_1 D_2 \cdot e^{D_2 \cdot (I_1 - 3)} \tag{C.2a}
\]
\[
\psi_D^{11} = \frac{\partial^2 \psi_D}{\partial I_1^2} = D_1 D_2^2 \cdot e^{D_2 \cdot (I_1 - 3)} \tag{C.2b}
\]

The derivatives of the proposed anisotropic SEF ($\psi_{GHO}$) are,

\[
\psi_{GHO}^m = \frac{\partial \psi_{GHO}}{\partial I_m} = \frac{k_1}{2k_2} \sum_{\alpha=1}^{N} \left( \frac{\partial e^{k_2 \langle E_\alpha \rangle^2}}{\partial I_m} \right) \tag{C.3a}
\]
\[
\psi_{GHO}^{mn} = \frac{\partial^2 \psi_{GHO}}{\partial I_n \partial I_m} = \frac{k_1}{2k_2} \sum_{\alpha=1}^{N} \frac{\partial}{\partial I_n} \left( \frac{\partial e^{k_2 \langle E_\alpha \rangle^2}}{\partial I_m} \right) \tag{C.3b}
\]

where,

\[
\frac{\partial e^{k_2 \langle E_\alpha \rangle^2}}{\partial I_m} = 2k_2 \langle E_\alpha \rangle \frac{\partial \langle E_\alpha \rangle}{\partial I_m} e^{k_2 \langle E_\alpha \rangle^2}
\]
\[
\frac{\partial^2 e^{k_2 \langle E_\alpha \rangle^2}}{\partial I_n \partial I_m} = 2k_2 \frac{\partial e^{k_2 \langle E_\alpha \rangle^2}}{\partial I_n} \left( \langle E_\alpha \rangle \frac{\partial \langle E_\alpha \rangle}{\partial I_m} \right) + 2k_2 e^{k_2 \langle E_\alpha \rangle^2} \frac{\partial}{\partial I_n} \left( \langle E_\alpha \rangle \frac{\partial \langle E_\alpha \rangle}{\partial I_m} \right) =
\]
\[
2k_2 e^{k_2 \langle E_\alpha \rangle^2} \left[ (2k_2 \langle E_\alpha \rangle^2 + 1) \frac{\partial \langle E_\alpha \rangle}{\partial I_n} \frac{\partial \langle E_\alpha \rangle}{\partial I_m} + \langle E_\alpha \rangle \frac{\partial^2 \langle E_\alpha \rangle}{\partial I_n \partial I_m} \right]
\]
\[
\frac{\partial \langle E_\alpha \rangle}{\partial I_1} = \kappa
\]
\[
\frac{\partial \langle E_\alpha \rangle}{\partial I_{4(aa)}} = 1 - 3\kappa
\]
\[
\frac{\partial^2 \langle E_\alpha \rangle}{\partial I_n \partial I_m} = 0, \forall (m, n)
\]

\[\text{(C.4)}\]

for all the sub-indices of the involved invariants ($\langle m, n \rangle \in [1, 4(11), 4(22), ...]$).

When 2 perfectly anisotropic family of fibers ($N = 2$) are considered ($\kappa = 0$),

\[
E_\alpha = I_{4(aa)} - 1
\]

\[\text{(C.5)}\]
and the derivatives become,

\[ \psi_{GHO}^{4(11)} = k_1^{(11)}(I_{4(11)} - 1) e^{k_2^{(11)}(I_{4(11)} - 1)^2} \]  
\[ \psi_{GHO}^{4(11)4(11)} = (k_1^{(11)} + 2k_1^{(11)} k_2^{(11)}(I_{4(11)} - 1)^2) e^{k_2^{(11)}(I_{4(11)} - 1)^2} \]  
\[ \psi_{GHO}^{4(22)} = k_1^{(22)}(I_{4(22)} - 1) e^{k_2^{(22)}(I_{4(22)} - 1)^2} \]  
\[ \psi_{GHO}^{4(22)4(22)} = (k_1^{(22)} + 2k_1^{(22)} k_2^{(22)}(I_{4(22)} - 1)^2) e^{k_2^{(22)}(I_{4(22)} - 1)^2} \]

where \((\alpha = 1, 2)\) represent both families of fibers, and \(I_{4(\alpha\alpha)}\) the in-plane contribution of the fiber (i.e. not out-of-plane interaction, \(I_{4(\alpha\beta)}\), is accounted for). Besides, different \((k_n^{(11)} \neq k_n^{(22)}, n = 1, 2)\) or equal \((k_n^{(11)} = k_n^{(22)} = k_n, n = 1, 2)\) properties can be assigned depending on the direction, giving freedom to define different behaviors in both preferential directions.

The derivatives of the volumetric SEF are,

\[ \psi_{vol}^J = \frac{1}{D} (J - \frac{1}{J}) \] (C.7a)
\[ \psi_{vol}^{JJ} = \frac{1}{D} \left( \frac{1}{J^2} + 1 \right) \] (C.7b)
\[ \psi_{vol}^{J J} = 2\kappa_0 (J - 1) \] (C.8a)
\[ \psi_{vol}^{JJ} = 2\kappa_0 \] (C.8b)

These constitutive equations can be directly implemented to simulate the soft tissue behavior of the cornea using an Abaqus user subroutine (UANISOHYPER.f). This subroutine only requires of the SEF and its derivatives.

```
subroutine uanisohyper_inv (ainv, ua, zeta, nfibers, ninv,
  ui1, ui2, ui3, temp, noel, cmname, incmpflag, ihybflag,
  numstatev, statev, numfieldv, fieldv, fieldvinc,
  numprops, props)
  include 'aba_param.inc'
character*80 cmname
  dimension ua(2), ainv(ninv), ui1(ninv),
  $ ui2(ninv*(ninv+1)/2), ui3(ninv*(ninv+1)/2),
  $ statev(numstatev), fieldv(numfieldv),
  $ fieldvinc(numfieldv), props(numprops)
```
real*8 C10,C01,C20,C11,C02,D1,D2
real*8 rk1,rk2,rkp4,rI40,rk3,rkp6,rI60,Dinv
real*8 om3kp,E_alpha1,E_alpha,ht4a,aux
real*8 half,zero,one,two,three,four,five,six,asmall
integer index_i1,index_i2,index_J,index_i4

C Modified HGO model: Neo Hookean + Demiray + Holzapfel (1/2 fiber families)
C
C W = C10(I1-3)+C01(I2-3)+C20(I1-3)^2+C11(I1-3)(I2-3)+C02(I2-3)^2
C + D1*[exp(D2(I1-3))-1]
C +(k1/k2)*[exp(k2*<kp4(I1-3)+(1-3kp4)(I4-I40)>^2)-1]
C +(k3/k4)*[exp(k4*<kp6(I1-3)+(1-3kp6)(I4-I40)>^2)-1]
C
C Neo Hookean parameters: C10, C01, C20, C11, C02
C Demiray Parameters: D1, D2
C Holzapfel fibers #1: rk1, rk2, rkp4, rI40 (crimping)
C Holzapfel fibers #2: rk3, rk4, rkp6, rI60 (crimping)
C ua : energies; ua(1): utot; ua(2): udev
C ainv: invariants; ui1 : dU/dI; ui2 : d2U/dIdJ; ui3 : d3U/dIdJdJ
C
C C10 = props(1)
C ISOTROPIC CONTRIBUTION: Neo Hookean + Demiray
C
aux2 = exp(D2*(ainv(index_i1)-three))
ua(2) = ua(2) + C10*(ainv(index_i1)-three)
* + C01*(ainv(index_i2)-three)
* + two * C20 * (ainv(index_i1)-three)
* + C11*(ainv(index_i1)-three)*D1 + D2 + aux2

C Derivatives of Isotropic Terms
C
C du/dI1
ui1(index_i1) = ui1(index_i1) + C10
* + two * C20 * (ainv(index_i1)-three)
* + C11 * (ainv(index_i2) - three) + D1 + D2 + aux2

C du/dI2
ui1(index_i2) = ui1(index_i2) + C01
* + two * C02 * (ainv(index_i2)-three)
* + C11 * (ainv(index_i1)-three)

C du/dI1I
ui2(index_i1,index_i1) = ui2(index_i1,index_i1)
* + two * C20 + D1 + D2 + aux2

C dI2/dI1I
ui2(index_i1,index_i2) = ui2(index_i1,index_i2)
* + two * C02

C dI2/dI1dI2
ui2(index_i1,index_i2) = ui2(index_i1,index_i2) + C11

C ANISOTROPIC CONTRIBUTION
C
C First family of fibers
C
if(nfibers>0) then
  om3kp = one - three * rkp4
  k1 = 1
  index_i4 = indxInv4(k1,k1)
  E_alpha1 = rkp4 * (ainv(index_i1) - three)
  * + om3kp * (ainv(index_i4) - rI40)
  E.alpha = max(E.alpha1, zero)
  ht4a = half + sign(half,E.alpha1 + asmall)
  aux = exp(rk2 * E.alpha * E.alpha)
C SEF function
  ua(2) = ua(2) + (rk1/(two*rk2))*(aux - one)
C Derivatives of the First family of fibers
C dU/dI1
  ui1(index_i1) = ui1(index_i1) + rk1 * rkp4 * aux * E.alpha
C dU/dI4
  ui1(index_i4) = rk1 * om3kp * aux * E.alpha
C dU/dI1dI1
  aux2 = ht4a + two * rk2 * E.alpha * E.alpha
  ui2(index(index_i1,index_i1)) = ui2(index(index_i1,index_i1))
  * + rk1 * rkp4 * rkp4 * aux * aux2
C dU/dI1dI4
  ui2(index(index_i1,index_i4)) = rk1 * rkp4 * om3kp * aux * aux2
C dU/dI2I1
  aux2 = ht4a + two * rk2 * E.alpha * E.alpha
  ui2(index(index_i1,index_i1)) = ui2(index(index_i1,index_i1))
  * + rk1 * rkp4 * rkp4 * aux * aux2
C dU/dI1dI4
  ui2(index(index_i1,index_i4)) = rk1 * rkp4 * om3kp * aux * aux2
C dU/dI2I6
  aux2 = ht4a + two * rk2 * E.alpha * E.alpha
  ui2(index(index_i1,index_i1)) = ui2(index(index_i1,index_i1))
  * + rk1 * rkp4 * rkp4 * aux * aux2
end if
C Second family of fibers
C
if(nfibers>1) then
  om3kp = one - three * rkp6
  k1 = 2
  index_i4 = indxInv4(k1,k1)
  E.alpha2 = rkp6 * (ainv(index_i1) - three)
  * + om3kp * (ainv(index_i4) - rI40)
  E.alpha = max(E.alpha2, zero)
  ht4a = half + sign(half,E.alpha2 + asmall)
  aux = exp(rk4*E.alpha*E.alpha)
C SEF function
  ua(2) = ua(2) + (rk3/(two*rk4))*(aux - one)
C Derivatives of Second family of fibers
C dU/dI1
  ui1(index_i1) = ui1(index_i1) + rk3 * rkp6 * aux * E.alpha
C dU/dI6
  ui1(index_i4) = rk3 * om3kp * aux * E.alpha
C dU/dI1dI1
  aux2 = ht4a + two * rk4 * E.alpha * E.alpha
  ui2(index(index_i1,index_i1)) = ui2(index(index_i1,index_i1))
  * + rk3 * rkp6 * rkp6 * aux * aux2
C dU/dI1dI6
  ui2(index(index_i1,index_i4)) = rk3 * rkp6 * om3kp * aux * aux2
C dU/dI2I6
  aux2 = ht4a + two * rk4 * E.alpha * E.alpha
  ui2(index(index_i1,index_i1)) = ui2(index(index_i1,index_i1))
  * + rk3 * rkp6 * rkp6 * aux * aux2


\[ u_{i2}(\text{index}_{i4},\text{index}_{i4}) = rk3 \times \text{om3kp} \times \text{om3kp} \times \text{aux} \times \text{aux2} \]

\text{end if}

\text{C COMPRESSIBILITY}

\text{C}

\text{if}(\text{incmpflag}.eq.0) \text{ then}
\begin{align*}
\text{det} &= \text{ainv}(\text{index}.J) \\
\text{ua}(1) &= \text{ua}(2) + \text{Dinv} \times ((\text{det} \times \text{det} - \text{one})/\text{two} - \log(\text{det})) \\
\text{ui1}(\text{index}.J) &= \text{Dinv} \times (\text{det} - \text{one}/\text{det}) \\
\text{ui2}(\text{index}(\text{index}.J,\text{index}.J)) &= \text{Dinv} \times (\text{one} + \text{one} / \text{det} / \text{det}) \\
&\text{if (hybflag.eq.1) then} \\
&\text{ui3}(\text{index}(\text{index}.J,\text{index}.J)) &= - \text{Dinv} \times \text{two} / (\text{det} \times \text{det} \times \text{det}) \\
&\text{end if}
\end{align*}
\text{end if}

\text{C GLOBAL END OF THE SUBROUTINE}

\text{RETURN}

\text{END}
C.2 Compressible Hyperelastic Constitutive Model: Modified Anisotropic

Recently, Nolan et al.\(^3\) reported that using the modified formulation of tensors (e.g. \(\tilde{\mathbf{C}}\)) results in an erroneous deformation (or stress state) when accounting for the anisotropic behavior of the fibers. To achieve a correct anisotropic behavior for compressible materials, they proposed to use the full right Cauchy-Green tensor for the definition of the anisotropy, whereas the isotropic contribution is kept dependent on the isochoric contribution.

The new constitutive model was implemented in a user subroutine (UMAT.f). Two tensors are required to define a UMAT subroutine properly: the Cauchy stress tensor (\(\mathbf{\sigma}\)) and the spatial tangent stiffness matrix (\(\mathbf{c}\)). As it can be found in any book of Continuum Mechanics,\(^4\) the deformation gradient (\(\mathbf{F}\)) and the right Cauchy-Green (\(\mathbf{C}\)) tensors are defined as,

\[
\mathbf{F} = \frac{\partial \mathbf{x}}{\partial \mathbf{X}} \quad \mathbf{C} = \mathbf{F}^T \mathbf{F} \quad (C.9)
\]

where \(\mathbf{x}\) stands for a point in the spatial (deformed, current, or Eulerian) configuration, and \(\mathbf{X}\) for the same point in the material (undeformed, reference, or Lagrangian) configuration.

Likewise, the second Piola-Kirchoff (\(\mathbf{S}\)), the Cauchy stress tensor (\(\mathbf{\sigma}\)), and the material tangent stiffness matrix (\(\mathbf{C}\)) are defined as,

\[
\mathbf{S} = \frac{2}{J} \frac{\partial \psi}{\partial \mathbf{C}} \\
\mathbf{\sigma} = \frac{1}{J} \mathbf{F} \mathbf{S} \mathbf{F}^T \\
\mathbf{C} = \frac{2}{J} \frac{\partial \mathbf{S}}{\partial \mathbf{C}} \quad (C.10)
\]

where \(\psi\) is the strain energy function (SEF) defining the material behavior, and \(J = \det \mathbf{F}\) is the elastic volume ratio.

According to the definition of the proposed SEF in sec.C.1, the second Piola-Kirchoff tensor remains,

\[
\mathbf{S} = \frac{2}{J} \left( \psi_1 \frac{\partial I_1}{\partial \mathbf{C}} + \psi_2 \frac{\partial I_2}{\partial \mathbf{C}} + \psi_3 \frac{\partial I_3}{\partial \mathbf{C}} + \psi_4 \frac{\partial I_4}{\partial \mathbf{C}} + \psi_5 \frac{\partial J}{\partial \mathbf{C}} \right) \quad (C.11)
\]

where the isotropic part is derived with respect to the isochoric contribution (\(\tilde{\mathbf{C}}\)), and the anisotropic part with respect to the full tensor (\(\mathbf{C}\)).
Accounting for the following mathematical definitions,

\[
\frac{\partial \boldsymbol{C}}{\partial \tilde{\boldsymbol{C}}} = \frac{1}{2} \mathbf{J} \mathbf{C}^{-1},
\]

\[
\frac{\partial \mathbf{I}}{\partial \tilde{\boldsymbol{C}}} = \mathbf{I} \mathbf{C}^{-1} = -\frac{1}{2} (\mathbf{C}^{-1} \mathbf{C} + \mathbf{C}^{-1} \mathbf{C})^T,
\]

\[
\frac{\partial \tilde{\boldsymbol{C}}}{\partial \mathbf{C}} = \mathbf{J}^{-2/3} \mathbf{P}^T = \mathbf{J}^{-2/3} \left[ \mathbf{I} - \frac{1}{3} \mathbf{C} \mathbf{C}^{-1} \right],
\]

\[\mathbf{[\bullet]}^\text{dev} = \mathbf{P} : (\bullet) = 6 (\bullet) : \mathbf{P}^T = (\bullet) - \frac{1}{3} ([\bullet] : \mathbf{C}) \mathbf{C}^{-1}\]

and letting the invariants be,

\[\tilde{I}_1 = tr(\tilde{\mathbf{C}}) = \mathbf{J}^{-2/3} tr(\mathbf{C}) = \mathbf{J}^{-2/3} I_1\]

\[I_{4(11)} = I_4 = \mathbf{A}_0, \text{ where index notation is simplified to } 4(11) = 4\]

\[I_{4(22)} = I_5 = \mathbf{B}_0, \text{ where index notation is simplified to } 4(22) = 6\]

\[
\frac{\partial \tilde{I}_1}{\partial \mathbf{C}} = \frac{\partial \tilde{I}_1}{\partial \tilde{\boldsymbol{C}}} : \frac{\partial \tilde{\boldsymbol{C}}}{\partial \mathbf{C}} = \mathbf{J}^{-2/3} \mathbf{[1]} = \mathbf{J}^{-2/3} \mathbf{[1]}^\text{dev} = \mathbf{J}^{-2/3} \left[ \mathbf{I} - \frac{1}{3} tr(\mathbf{C}) \mathbf{C}^{-1} \right]
\]

\[
\frac{\partial I_4}{\partial \mathbf{C}} = \mathbf{A}_0, \text{ where } \mathbf{A}_0 = \mathbf{a}_0 \otimes \mathbf{a}_0 \text{ (the 1st fiber direction)}
\]

\[
\frac{\partial I_5}{\partial \mathbf{C}} = \mathbf{B}_0, \text{ where } \mathbf{B}_0 = \mathbf{b}_0 \otimes \mathbf{b}_0 \text{ (the 2nd fiber direction)}
\]

(C.13)

the second Piola-Kirchhoff (note the index notation simplification 4(11) = 4, 4(22) = 6) results in,

\[
\mathbf{S} = 2 \left[ \mathbf{J}^{-2/3} \mathbf{[1]} + \frac{1}{3} tr(\mathbf{C}) \mathbf{C}^{-1} \right]
\]

where \(\mathbf{P} = \left[ \mathbf{I} - \frac{1}{3} \mathbf{C} \mathbf{C}^{-1} \right]\) is the Projection tensor, \(^7\) and \([\bullet]^\text{dev}\) is the correct deviatoric operator in the material configuration.

The Cauchy stress tensor will arise from the push-forward of the second Piola-Kirchhoff stress tensor from the material to the spatial configuration as,

\[
\mathbf{\sigma} = \frac{1}{\mathbf{J}} \mathbf{FSF}^T
\]

\[
\mathbf{\sigma} = \frac{2}{\mathbf{J}} \left[ \mathbf{[1]} + \frac{1}{3} \mathbf{[1]} \right] + \frac{1}{3} \mathbf{[1]} \] (C.15)

where \(\mathbf{\tilde{b}}\) is the modified left Cauchy-Green tensor in the spatial configuration \((\mathbf{\tilde{b}} = \mathbf{J}^{-2/3} \mathbf{b} = \mathbf{J}^{-2/3} \mathbf{F} \mathbf{F}^T)\), and \(\mathbf{A}\) (or \(\mathbf{B}\)) is the push-forwarded tensor associated with the direction of the fibers in the spatial configuration \((\mathbf{A} = \mathbf{F} \mathbf{A}_0 \mathbf{F}^T)\).

\(^6\) Holzapfel 2000
Now, following the same procedure, the tangent stiffness matrix in the reference configuration is,

$$ C = 2 \frac{\partial S}{\partial \mathbf{C}} = $$

\[
4 \tilde{\psi}_1 J^{-2/3} \frac{\partial}{\partial \mathbf{C}} \left( 1 - \frac{1}{3} I_1 \mathbf{C}^{-1} \right) + 4 \left[ J^{-2/3} \tilde{\psi} \left( \frac{\partial I_1}{\partial \mathbf{C}} : \frac{\partial \mathbf{C}}{\partial \mathbf{C}} \right) + \tilde{\psi} \frac{\partial (J^{-2/3})}{\partial \mathbf{C}} \right] \otimes (1 - \frac{1}{3} I_1 \mathbf{C}^{-1})
\]

\[
+ 4 \left[ \psi_{44} \frac{\partial I_4}{\partial \mathbf{C}} \otimes \mathbf{A}_0 + \psi_{66} \frac{\partial I_6}{\partial \mathbf{C}} \otimes \mathbf{B}_0 \right]
\]

\[
+ 2 \left[ J \psi_{ij} \frac{\partial J}{\partial \mathbf{C}} \otimes \mathbf{C}^{-1} + \psi_{ij} \frac{\partial \mathbf{C}}{\partial \mathbf{C}} \otimes \mathbf{C}^{-1} + J \psi_{ij} \frac{\partial \mathbf{C}}{\partial \mathbf{C}} \right]
\]

\[
= 4 \frac{J^{-2/3}}{3} \left[ 3J^{-2/3} \tilde{\psi} \left( 1 - \frac{1}{3} I_1 \mathbf{C}^{-1} \right) - \tilde{\psi} \mathbf{C}^{-1} \right] \otimes (1 - \frac{1}{3} I_1 \mathbf{C}^{-1})
\]

\[
- J^{-2/3} \frac{\tilde{\psi}_1}{3} (1 \otimes \mathbf{C}^{-1} + I_1 \mathbf{I}^{-1})
\]

\[
+ 4 \left[ \psi_{44} \mathbf{A}_0 \otimes \mathbf{A}_0 + \psi_{66} \mathbf{B}_0 \otimes \mathbf{B}_0 \right]
\]

\[
+ J (\psi_{ij} + \psi_{ij}) \mathbf{C}^{-1} \otimes \mathbf{C}^{-1} + 2 J \psi_{ij} \mathbf{I}^{-1}
\]

Finally, the spatial tangent stiffness matrix (c) is given by the push-forward of the material tangent stiffness matrix as,

$$ c = \frac{1}{J} \mathbf{F} \otimes \mathbf{F} : \mathbf{C} : \mathbf{F}^T \otimes \mathbf{F}^T $$

$$ c_{ijkl} = \frac{1}{J} F_{ip} F_{jq} C_{pqr} F_{kr} F_{ls} \quad (C.17) $$

The push-forward of the fourth-order different terms are,

- **F⊗F : (1 ⊗ 1) : F^T ⊗ F^T**

  In index notation,

  $$ F_{ip} F_{jq} (\delta_{pq} \delta_{rs}) F_{kr} F_{ls} = F_{iq} F_{jq} F_{ks} F_{ls} = 8 $$

  $$ (\mathbf{F}^T)_{ij} \otimes (\mathbf{F}^T)_{kl} = (\mathbf{b} \otimes \mathbf{b})_{ijkl} \quad (C.18) $$

  \(^a\) Contraction with delta of Kronecker.

- **F⊗F : (1 ⊗ C^-1) : F^T ⊗ F^T**
In index notation,

\[
F_{ip}F_{jq}(\delta_{pq}C^{-1}_{rs})F_{kr}F_{is} = F_{iq}F_{jr}C^{-1}_{rs}F_{kr}F_{is} = F_{iq}F_{jr}(F_{rm}^{-1}F_{sm}^{-1})F_{kr}F_{is} = 9
\]

\[
F_{iq}F_{jr}(F_{kr}F_{rm}^{-1})(F_{is}F_{sm}^{-1}) = 10F_{iq}F_{jr}\delta_{km}\delta_{lm} = F_{iq}F_{jr}\delta_{kl} = (FF^T)_{ij}1_{kl} = (b \otimes 1)_{ijkl}
\]  

(C.19)

\[^sC^{-1} = (F^T)^{-1} = F^{-1}F^{-T} \]

\[^{10}F_{im}F_{mj}^{-1} = \delta_{ij} \rightarrow FF^{-1} = 1 \]

- \(F \otimes F : (C^{-1} \otimes C^{-1}) : F^T \otimes F^T\)

In index notation,

\[
F_{ip}F_{jq}(C^{-1}_{pq}C^{-1}_{rs})F_{kr}F_{is} = \\
F_{ip}F_{jq}(C^{-1}_{pq}C^{-1}_{rs})F_{kr}F_{is} = \\
F_{ip}F_{jq}(C^{-1}_{pq}C^{-1}_{rs})F_{kr}F_{is} = F_{ip}F_{jq}[\frac{1}{2}(C^{-1}_{pr}C^{-1}_{qs} + C^{-1}_{ps}C^{-1}_{qr})]F_{kr}F_{is} = \\
F_{ip}F_{jq}[\frac{1}{2}(C^{-1}_{pr}C^{-1}_{qs} + C^{-1}_{ps}C^{-1}_{qr})]F_{kr}F_{is} = F_{ip}F_{jq}[\frac{1}{2}(F^{-1}_{pr}F^{-1}_{qs}) + (F^{-1}_{ps}F^{-1}_{qr})]F_{kr}F_{is} = \\
F_{ip}F_{jq}[\frac{1}{2}(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})] = \frac{1}{2}((1 \otimes 1)_{ijkl} + (1 \otimes 1)_{ijkl}) = -I_{ijkl}
\]

After some algebra, \(c\) in tensorial notation is,

\[
c = c_{\text{Isotropic}} + c_{\text{Anisotropic}} + c_{\text{Volumetric}}
\]

where,

\[
c_{\text{Isotropic}} = \frac{4\psi_1}{3f}I + \frac{4\psi_{11}}{f}b \otimes b
\]

\[
+ \frac{4}{3f}(\psi_{11}I + \psi_1)[\frac{I}{3}(1 \otimes 1) - (b \otimes 1 + 1 \otimes b)]
\]

\[
c_{\text{Anisotropic}} = \frac{4}{f}(\psi_{44}A \otimes A + \psi_{66}B \otimes B)
\]

\[
c_{\text{Volumetric}} = (J\psi_{ff} + \psi_J)(1 \otimes 1) - 2\psi_JI
\]

(C.22)
C.3 Implementation of UMAT for Compressible Material (Modified Anisotropic)

Linearization: Taylor Series and Directional Derivative

To linearize a nonlinear and smooth function in the material description $\Gamma = \Gamma(x)$, which can be a scalar-valued, vector-valued, or tensor-valued, the Taylor’s expansion can be used as,

$$
\Gamma(x) = \Gamma(x_0) + \frac{\partial \Gamma(x)}{\partial x} |_{x=x_0} (x - x_0) + \frac{1}{2!} \frac{\partial^2 \Gamma(x)}{\partial x^2} |_{x=x_0} (x - x_0)^2 + ... \quad \text{(C.23)}
$$

where $\Gamma$ is a scalar-valued function of a vector $x$ (scalar-valued vector function). Let $x$ be the sum of a known fixed point $x_0$, and an infinitesimal linear increment $\Delta x$ ($x = x_0 + \Delta x$). Truncating at the first-order term of the Taylor’s expansion, $\Gamma$ can be approximated as,

$$
\Gamma(x) \approx \Gamma(x_0) + \frac{\partial \Gamma(x)}{\partial x} |_{x=x_0} (x - x_0)
$$

$$
\Gamma(x_0 + \Delta x) \approx \Gamma(x_0) + \frac{\partial \Gamma(x)}{\partial x} |_{x=x_0} (\Delta x) \quad \text{(C.24)}
$$

where $\Gamma(x_0)$ approximates the solution for a given state $x_0$, and $\frac{\partial \Gamma(x)}{\partial x} |_{x=x_0} (\Delta x)$ is the linear change of $\Gamma$ due to the linear perturbation $\Delta x$ at $x_0$. Furthermore, this linear change can be also defined as the Directional Derivative of $\Gamma$ at a given (fixed) point ($x_0$) in the direction of the incremental ‘variable’ field ($\Delta x$) or, by analogy, the linearization of $\Gamma$ at $x_0$.

The Directional Derivative can be defined using the Gâteaux operator ($D(\bullet)$) as,

$$
D_{\Delta x}(\Gamma(x)) \triangleq \frac{d}{de} (\Gamma(x + e\Delta x)) |_{e=0}
$$

applying the chain rule,

$$
\frac{d}{de} (\Gamma(x(e))) |_{e=0} = \frac{\partial \Gamma(x)}{\partial x} \cdot \frac{\partial x(e)}{\partial e} |_{e=0} = \nabla \Gamma(x) \cdot \Delta x \quad \text{(C.26)}
$$

Then, the linearization operator can be defined as $\Delta(\bullet) = D_{\Delta x}(\bullet) = \nabla(\bullet) \cdot \Delta x$. 

â£¥£¥
Material Time Derivative

The time derivative of a scalar-valued vector function $(\Gamma(X, t))$ in the material (reference) configuration can be defined as,

$$\dot{\Gamma} = \frac{D\Gamma(X, t)}{Dt} = \left(\frac{\partial \Gamma(X, t)}{\partial t}\right)_X$$

(C.27)

where the subindex $X$ denotes the variable that is held constant while taking the partial derivative of $\Gamma$.

Furthermore, the relation between the material time derivative and the directional derivative in the direction of the velocity vector field $(V)$ is given by the definition of the directional derivative, and the chain rule as,

$$\frac{D\Gamma(X, t)}{Dt} \equiv D_V \Gamma(X, t) = \frac{d}{d\epsilon} \Gamma(X + \epsilon V, t)|_{\epsilon=0} =$$

$$\frac{\partial \Gamma(X, t)}{\partial X} \cdot \frac{\partial X(\epsilon)}{\partial \epsilon} = \frac{\partial \Gamma(X, t)}{\partial t}_X \cdot V = \left(\frac{\partial \Gamma(X, t)}{\partial t}\right)_X$$

(C.28)

where, $V = \frac{\partial X}{\partial t}$

Applying the concept of directional derivative in the direction of the velocity field $v$ (spatial configuration)\(^{12}\) at position $x$ to the deformation gradient $(F = \frac{\partial x}{\partial X})$,

$$\dot{F} = D_v F = \frac{d}{d\epsilon} \left(\frac{\partial (x + \epsilon v)}{\partial X}\right)_{\epsilon=0} = \frac{d}{d\epsilon} \left(F + \epsilon \frac{\partial v}{\partial X}\right)_{\epsilon=0} =$$

$$\frac{\partial v}{\partial X} = \frac{\partial v}{\partial x} \cdot \frac{\partial x}{\partial X} = \frac{\partial v}{\partial x} \cdot F$$

(C.29)

from which the following important relation is derived,

$$\dot{F} = \frac{\partial v}{\partial x} \cdot F = \ell \cdot F$$

(C.30)

where $\ell$ is the spatial velocity gradient tensor. Additionally, from $\ell$ can be also derived the (symmetric) rate-of-deformation tensor $(D)$, and the (anti-symmetric) spin tensor (or rate-of-rotation tensor),

$$D = \frac{1}{2}(\ell + \ell^T)$$

$$W = \frac{1}{2}(\ell - \ell^T)$$

(C.31)
Co-rotational Derivative of the Cauchy Stress Tensor

To implement a user material using an UMAT subroutine (Abaqus), it is necessary to provide the co-rotational derivative of the Cauchy stress tensor. When solving the variation of Potential Energy, Abaqus is using a co-rotational formulation to determine the Jacobian matrix. In this vein, the derivative of the Kirchoff stress tensor is solved using the Jaumann-Zaremba rate,\(^{13}\)

\[
\dot{\tau} = \tau_j + W \cdot \tau + \tau \cdot W^T
\]  

(C.32)

where \(W\) is the anti-symmetric spin tensor defined as the anti-symmetric contribution of the spatial velocity gradient (\(\ell\)), \(\dot{\tau}\) is the time derivative of the Kirchoff stress tensor, and \(\tau_j\) is the Jaumann-Zaremba rate of the Kirchoff stress tensor.

Deriving the Kirchoff stress tensor with respect to time,

\[
\tau = FSF^T
\]

\[
\dot{\tau} = \dot{FSF}^T + F\dot{SF}^T + FSF^T \equiv D_v \dot{\tau} 
\]  

(C.33)

and using the relation \(\dot{F} = \ell F\),\(^{14}\) the linearization of \(\tau\) can be expressed as,

\[
D_v \dot{\tau} = \dot{\tau} = \ell \tau + F\dot{SF}^T + \tau \ell^T
\]  

(C.34)

where \(F\dot{SF}^T\) is the Truesdell derivative, or Truesdell rate (\(\tau_T\)).

Equaling both expressions of \(\dot{\tau}\), and knowing that \(\ell = D + W\),

\[
\tau_j + W\tau + \tau W^T = \ell \tau + F\dot{SF}^T + \tau \ell^T
\]

(C.35)

where only the time derivative of \(S\) needs to be linearized,

\[
\dot{S} = \frac{DS}{Dt} = \frac{\partial S}{\partial C} : \frac{\partial C}{\partial t} = \frac{\partial S}{\partial C} : D_v C
\]  

(C.36)

developing the directional derivative \(D_v C\) as,

\[
D_v C = D_v (F^T F) = D_v (F^T) F + F^T D_v (F) = F^T (\ell + \ell^T) F = F^T (2D) F
\]  

(C.37)

\(^{15}\) \(D_v (F) = \ell F\)
Finally, we can express the Truesdell derivative ($\tau_T$) as the double contraction of the spatial tangent stiffness matrix and the rate-of-deformation tensor,

$$
\tau_T = F F^T = F \left( 2 \frac{\partial S}{\partial C} : (F^T DF) \right) F^T = 16
$$

$$
F \left( C : (F^T DF) \right) F^T = \left( \otimes F : F : \otimes F^T \right) : D = \epsilon^T : D
$$

or in index notation,

$$
(\tau_T)_{ij} = F_{ip} \left( C : (F^T DF) \right)_{pq} F_{jq} = F_{ip} \left( C_{pqrs} (F^T DF)_{rs} \right) F_{jq} = F_{ip} \left( C_{pqrs} (F_{nr} D_{nm} F_{ms}) \right) F_{jq} = (F_{ip} F_{jq} F_{nr} F_{ms} C_{pqrs}) D_{nm} = \epsilon^T_{ijmn} D_{nm}
$$

where $\epsilon^T$ is the spatial stiffness matrix derived from the Kirchhoff stress tensor (i.e. the push-forward does not account for the jacobian as when it is derived from the Cauchy stress tensor$^{17}$).

Then, the Jaumann-Zaremba rate remains,

$$
\tau_J = \epsilon^T : D + D \tau + \tau D^T
$$

After some simple algebra,

$$
D \tau = D_{ik} \tau_{kj}
$$

where,

$$
D_{ik} = I_{ikpq} D_{pq} = (I : D)_{ik}
$$

and,

$$
I_{ikpq} = \frac{1}{2} (\delta_{ip} \delta_{kq} + \delta_{iq} \delta_{kp}) \text{ symmetric 4th order identity tensor}
$$

then,

$$
D_{ik} \tau_{kj} = \frac{1}{2} (\delta_{ip} \delta_{kq} + \delta_{iq} \delta_{kp}) D_{pq} \tau_{kj} = \frac{1}{2} (\tau_{iq} \delta_{ip} + \delta_{ij} \tau_{pq}) D_{pq}
$$

and, analogously,

$$
\tau D^T = \tau_{ik} D_{jk}
$$

where,

$$
D_{jk} = I_{jkpq} D_{pq}
$$

and,

$$
I_{jkpq} = \frac{1}{2} (\delta_{jp} \delta_{kq} + \delta_{jq} \delta_{kp}) \text{ symmetric 4th order identity tensor}
$$

then,

$$
\tau_{ik} D_{jk} = \frac{1}{2} (\delta_{jp} \delta_{kq} + \delta_{jq} \delta_{kp}) D_{pq} \tau_{ik} = \frac{1}{2} (\tau_{iq} \delta_{jp} + \delta_{ij} \tau_{ip}) D_{pq}
$$

$D \tau + \tau D^T$ can be simplified as,

$$
D \tau + \tau D^T = \mathbb{H}^T : D
$$
and, eventually, the Jaumann-Zaremba is simplified as,

\[ \tau_J = (\varepsilon^T + \mathbf{H}^T) : \mathbf{D} \]

with,

\[ \mathbf{H}_{ijkl}^T = \frac{1}{2} \left( \tau_{jl} \delta_{ik} + \tau_{jk} \delta_{il} + \tau_{il} \delta_{jk} + \tau_{ik} \delta_{jl} \right) \]

\[ \text{(C.44)} \]

However, since this rate is derived from the Kirchoff stress tensor, the implementation does not account for the jacobian of the push-forward of the Cauchy stress tensor \( (\tau = \int \sigma) \). Hence, the correct definition of the tensors involved in the definition of the UMAT are,

\[ \varphi_{\text{UMAT}} = \frac{1}{J} (\varepsilon^T + \mathbf{H}^T) = \varepsilon + \mathbf{H}^\sigma \]

\[ \text{with, } \mathbf{H}_{ijkl}^\sigma = \frac{1}{2} \left( \sigma_{jl} \delta_{ik} + \sigma_{jk} \delta_{il} + \sigma_{il} \delta_{jk} + \sigma_{ik} \delta_{jl} \right) \]

\[ \text{(C.45)} \]

**Push-Forward of Collagen Fibers**

Apart from undergoing a deformation, the orientation of the fibers will displace and rotate with the material point as the average of the rigid body motion. As the UMAT is solved in a local system oriented with the local orientation of the fiber (see in Figure C.1.b), the initial local fiber reference will be always the same (i.e. the local fiber direction in the material configuration). Therefore, the fiber orientation needs to be updated using the deformation gradient from the material to the spatial configuration (see in Figure C.1.b-c).

In the present case, the first fiber is aligned with the A-axis (i.e. 1-axis) of the local coordinate system of the material (reference) configuration \( (ABC) \). The second fiber is aligned with the A-axis, and the second fiber is rotated \( \alpha \) with respect to the first one. Fibers are push-forwarded from its definition in the material configuration to the current (spatial) configuration \( (abc) \) by means of the deformation gradient \( \mathbf{F} \).

Figure C.1: Push-forward of the fibers (UMAT). (a) Collagen fibers will not be defined in the Global Coordinate system \( (XYZ) \) as in the UANISHYPER subroutine, but they will be defined in a material Local Coordinate system \( (ABC) \); (b) Fibers are assumed to have an in-plane distribution, defining the first fiber \( f_1^{ABC} \) as a vector (e.g. aligned with A-axis), and the second fiber \( f_2^{ABC} \) with a rotation \( \alpha \) with respect to the first one; (c) Fibers are push-forwarded from its definition in the material configuration to the current (spatial) configuration \( (abc) \) by means of the deformation gradient \( \mathbf{F} \).
fiber is defined to be co-planar, and rotated an angle ($\alpha$) with respect to the first one. When the element deforms and displaces, collagen fibers need to be updated from the material to the spatial configuration by means of the deformation gradient ($F$).

A feasible pseudo-code to update the organization of the collagen fibers is,

```plaintext
function pushforward_fibers(DFGRD1, PROPS, FIBER, A, B)
    C Function to perform the pushforward of a vector
    C Input:
    C - Deformation gradient (DFGRD1)
    C - Properties (PROPS)
    C - Fiber orientation (FIBER)
    C Output:
    C - A, B: material tensors of fiber orientations used in the SEF
    C Definition of variables
    alpha = PROPS(1)
    a0 = FIBER(1:3)
    b0 = FIBER(4:6)
    C Update fibers
    a = matmul(DFGRD1, a0)
    b = matmul(DFGRD1, b0)
    C Tensors of fibers
    A = matmul(a, a)
    B = matmul(b, b)
    return
end
```

Since Abaqus 6.14, arrays can be managed by in-built functions (i.e. Allocatable Arrays) that provide the meaningful functionality: loading the fibers at the beginning of the simulation, creating pointers to this arrays, and calling them inside different functions. Contrarily to former versions, this neat solution avoids problems when performing parallel computation. To load an external file containing the orientation of the fibers, we need a subroutine to handle external databases (UEXTERNALDB.f). To define these in-built functions inside the subroutine is necessary,

- to call the utility library,

  ```plaintext
  SUBROUTINE UEXTERNALDB(LOP,LRESTART,TIME,DTIME,KSTEP,KINC)
  #INCLUDE<SMAAspUserSubroutines.hdr>
  ```

- to define the pointers and the array variables where the fibers will be stored,

  ```plaintext
  integer :: KELEM = 666 C Number of elements
  integer :: COMPS = 3 C Number of components (3D -> 3)
  integer :: NFAM = 2 C Number of families of fibers (0, 1, 2,...)
  real*8, dimension(KELEM*COMPS*NFAM) :: FIBERS C Create Array
  pointer(ptrF, FIBERS) C Assign pointer to array
  ```
• (only at the beginning of the simulation) first to allocate the memory that will consume the pointer and to assign its identity number (i.e. an integer). Second, to transfer the information from the file where the orientation of the fibers are defined to the array.

```fortran
if(LOP.EQ.0) then
  C Create pointer (pointer ID, size of array)
  ptrF = SMALocalFloatArrayCreate(2, int(KELEM*COMPS*NFAM))
  CALL GETOUTDIR(JOBDIR, LENJOBDIR)
  FILENAME = JOBDIR(:LENJOBDIR) // '/orientation.inp' C Load file of fibers
  open(9, file=FILENAME)
  do I=1,KELEM C Copy all orientations to array
    index1=(I-1)*NFAM*COMPS+1
    index2=index1+NFAM*COMPS-1
    C Transfer fibers from file to array)
    read(9,*) (FIBERS(J), J=index1,index2)
  end do
  close(9)
```

Once defined, these allocatable arrays can be called from other subroutine (e.g. UMAT.f) using the memory pointers,

```fortran
C Label and components of the elements of Thread-Arrays
  real*8, dimension(KELEM*COMPS*NFAM) :: FIBRES
  pointer(ptrF,FIBRES)
C C Call Thread-Array pointers using the pointer ID
C ptrF = SMALocalFloatArrayAccess(2)
C Now FIBERS contains the information load at the beginning!
```

### C.4 Validation of the Implementation of a Constitutive Model

Let us consider a traditional strain energy function ($\psi$) that describes the nearly-incompressible anisotropic (2 families of fibers) behavior of a material. Then, a consistent splitting into volumetric and isochoric parts can be applied ($\psi = \psi_{vol}(J) + \psi_{isoch}(I_1, I_4, I_6)$). As a result, we can apply a multiplicative decomposition to the deformation gradient as, $F = (J^{1/3}) \tilde{F}$, where $J^{1/3}$ corresponds to the volume-changing deformation, and $\tilde{F}$ corresponds to the volume-preserving deformation ($\det F = 1$). Consequently, the second Piola-Kirchhoff stress tensor can be expressed as, $S = S_{vol} + \tilde{S}_{isoch}$.

The general Cauchy stress tensor in hyperelasticity is given by,

$$\sigma = J^{-1} \frac{\partial \psi(F)}{\partial F} F^T$$  \hspace{1cm} (C.46)
Besides, when the material is considered as incompressible, it is referred to as a constrained material and subjected to the incompressibility condition \((J = 1)\). Then, the general constitutive equation for incompressible materials is,

\[
\psi = \psi(F) - p(J - 1)
\]

where \(p\) is the hydrostatic pressure, acting as Lagrange multiplier.

Hence, the Cauchy stress tensor for incompressible materials is,

\[
\sigma = -p1 + \frac{\partial \psi(F)}{\partial F} F^T = -p1 + J^{-1} FSF^T
\]

where \(p\) is unknown, and it can only be determined from the equilibrium equations and the boundary conditions (e.g. with the condition \(\sigma_{22} = 0\) in uniaxial tensile tests). On the contrary, when a compressible material is studied, \(p\) is specified by a constitutive equation \((p = \frac{d \psi_{vol}(J)}{dJ})\) since deformations can also arise from volume changes (oppositely to incompressible materials).

Eventually, particularizing the Cauchy stress tensor to the general strain energy function (SEF), and accounting for the incompressibility restriction \((J = 1)\),

\[
\sigma = -p1 + 2(\psi_1 \tilde{b} + \psi_4 n \otimes n + \psi_6 m \otimes m)
\]

where \(\psi_1\), \(\psi_4\), and \(\psi_6\) are the derivatives of the SEF with respect to the modified first, and fourth invariants (e.g. \(I_1 = J^{2/3} \bar{I}_{1}\), equal when incompressibility is accounted for), \(\tilde{b} = J^{2/3} \bar{b}\) is the left Cauchy-Green tensor, \(n = (n_1, n_2, n_3)\) is the spatial direction of the first family of fibers, and \(m = (m_1, m_2, m_3)\) is the spatial direction of the second family of fibers \((n = F_{n0}, m = F_{m0})\).

After implementing any constitutive model in a subroutine, its validation is necessary to ensure that the subsequent Finite Element simulations are not erroneous. In order to do that, analytic solutions and computational simulations of basic problems are compared.

**Uniaxial and Biaxial Tests**

In a pure uniaxial test, the sample is equally pulled along the symmetry axis (see in Figure C.2). Under this conditions, the displacement field along the \(x\)-axis (horizontal axis) is,

\[
x = \lambda X
\]

where \(x\) is the coordinate of the point in the current configuration, \(X\) is the coordinate of the point in the reference configuration, and \(\lambda\) is the proportional stretch along the axis. In the free boundaries, the sample will compress an unknown amount \((\lambda^*_2, \lambda^*_3)\). Assuming that the sample will compress equally along the unloaded axes \((\lambda^*_2 = \lambda^*_3 = \lambda^*)\), the deformation gradient will be given by,
Taking into account the preservation of volume, the determinant of the deformation gradient must be 1 ($J = \det F = 1$). Hence,

$$\det F = \lambda (\lambda^*)^2 = 1$$

$$\lambda^* = \frac{1}{\sqrt{\lambda}} \quad \text{(C.51)}$$

and, subsequently, the deformation gradient ($F$) and the left Cauchy-Green ($b$) tensors are,

$$F = \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \frac{1}{\sqrt{\lambda}} & 0 \\ 0 & 0 & \frac{1}{\sqrt{\lambda}} \end{bmatrix}, \quad b = \begin{bmatrix} \lambda^2 & 0 & 0 \\ 0 & \frac{1}{\lambda} & 0 \\ 0 & 0 & \frac{1}{\lambda^2} \end{bmatrix}$$

Regarding biaxial tests, the displacements along the x-axis (horizontal axis) and y-axis (vertical axis) are controlled (see in Figure C.3). Then, the displacement field is given by,

$$x = \lambda X + \mu Y$$

$$y = \mu X + \lambda Y$$

(C.52)

where $(x, y)$ are the current coordinates of a point, $(X, Y)$ are the reference coordinates of the same point, and $(\lambda, \mu)$ are the stretches in horizontal and vertical direction respectively.

Accounting for the volume preservation, the deformation gradient ($F$) and the left Cauchy-Green ($b$) tensors are,

$$F = \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \mu & 0 \\ 0 & 0 & \frac{1}{\mu X} \end{bmatrix}, \quad b = \begin{bmatrix} \lambda^2 & 0 & 0 \\ 0 & \mu^2 & 0 \\ 0 & 0 & \frac{1}{\mu^2 \lambda^2} \end{bmatrix}$$

Generally, in a triaxial tensile test, all deformations along the main axes are different. Then, the general deformation gradient and the general left Cauchy-Green tensors are,

$$F = \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \mu & 0 \\ 0 & 0 & \nu \end{bmatrix}, \quad b = \begin{bmatrix} \lambda^2 & 0 & 0 \\ 0 & \mu^2 & 0 \\ 0 & 0 & \nu^2 \end{bmatrix}$$
Considering (C.49), the analytic solution of the Cauchy stress in a triaxial tensile test is,

\[
\begin{align*}
\sigma_{11} &= -p + 2 \left( \psi_1 \lambda^2 + \psi_4 n_1^2 + \psi_6 m_1^2 \right) \\
\sigma_{22} &= -p + 2 \left( \psi_1 \mu^2 + \psi_4 n_2^2 + \psi_6 m_2^2 \right) \\
\sigma_{33} &= -p + 2 \left( \psi_1 \nu^2 + \psi_4 n_3^2 + \psi_6 m_3^2 \right) \\
\tau_{12} &= \psi_4 n_1 n_2 + \psi_6 m_1 m_2 \\
\tau_{13} &= \tau_{23} = 0 \text{ if fibers are in plane 1-2}
\end{align*}
\] (C.53)

Analytic solution of uniaxial and biaxial tests can be derived from this general solution by applying the following restrictions,

- **Uniaxial tests:** \( \mu = \nu = 1 / \sqrt{\lambda} \), the hydrostatic pressure \( p \) is obtained applying the restriction \( \sigma_{22} = 0 \) \((p = 2 \left( \psi_1 \mu^2 + \psi_4 n_2^2 + \psi_6 m_2^2 \right))\), \( \sigma_{33} = 0 \), and \( \tau_{13} = \tau_{23} = 0 \) if fibers are contained in plane 1-2.

- **Biaxial tests:** \( \nu = 1 / (\lambda \mu) \), the hydrostatic pressure \( p \) is obtained applying the restriction \( \sigma_{33} = 0 \) \((p = 2 \left( \psi_1 \nu^2 + \psi_4 n_3^2 + \psi_6 m_3^2 \right))\), and \( \tau_{13} = \tau_{23} = 0 \) if fibers are contained in plane 1-2.

**Optimization Procedure**

To obtain the analytic solution (i.e. stresses), it is necessary to carry out an optimization, in which we can distinguish,

- **Parameters:** material parameters defining the constitutive behavior \((\psi)\), angle of the fibers \((\alpha, \theta)\), geometry (unit cube).

- **Variables:** stretches \((\lambda, \mu, \nu)\)

**Uniaxial test**

The control variable is the stretch along the pulling axis \((\lambda)\) during a displacement-controlled test. The material parameters \((\psi)\), and the angle between fibers in the material configuration \((\alpha, \theta)\) are known. Then, only the deformations in the transverse axes to the pull are unknown \((\mu, \nu)\).

The minimization problem is,

\[
\operatorname{argmin}_{\mu, \nu} \sigma^*(\lambda, \mu, \nu, \psi, \alpha, \theta) = 0
\]

where, \( \sigma^* = [\sigma_{22}, \sigma_{33}] \) (C.54)
Once the unknown stretches \((\mu, \nu)\) are determined, the Cauchy stress in normal \((\sigma_{11})\) and shear \((\tau_{12})\) directions are directly calculated.

**Biaxial test**

The control variables are the stretches along the pulling axes \((\lambda, \mu)\) during a displacement-controlled test. The material parameters \((\psi)\), and the angle between fibers in the material configuration \((\alpha, \theta)\) are known. Then, only the deformation in the transverse axis to the plane of pull is unknown \((\nu)\).

The minimization problem is,

\[
\arg\min_{\nu} \sigma_{33}(\lambda, \mu, \psi, \alpha, \theta) = 0 \tag{C.55}
\]

Once the unknown stretch \((\nu)\) is determined, the Cauchy stress in normal \((\sigma_{11}, \sigma_{22})\) and shear \((\tau_{12})\) directions are directly calculated.

**Pure Isochoric Shear Test**

In a pure shear test with volume preservation (isochoric), one of the sides of the sample is displaced laterally while the opposite is restrained (see in Figure C.4). Then, the Jacobian is always the unit \((J = 1)\), and the Lagrangian penalty term does not apply \((p(J - 1) = 0)\). Under this conditions, the displacement field is,

\[
x = X + Y\sin(\gamma)
\]

where, \(\sin(\gamma) = \frac{U_{\tau}}{L_0} = U_{\tau}\) when the length is the unit

and, \(\sin(\gamma) = U_{\tau}\) when the length is the unit

\[
y = Y
\]

where \(\gamma\) is the deformation angle between the material and spatial configuration, \(L_0\) is the lateral dimension of the sample in the material configuration, and \(U_{\tau}\) is the displacement applied in the moving boundary.

Analogously to uniaxial and biaxial tests, and accounting for the volume preservation, the deformation gradient and the left Cauchy-Green tensors are,

\[
F = \begin{bmatrix}
1 & \sin(\gamma) & 0 \\
0 & 1 & 0 \\
0 & 0 & 1
\end{bmatrix}, \quad b = \begin{bmatrix}
1 + \sin^2(\gamma) & \sin(\gamma) & 0 \\
\sin(\gamma) & 1 & 0 \\
0 & 0 & 1
\end{bmatrix}
\]
After some algebra, the analytic solution of the Cauchy stress is,

\[
\sigma_{11} = 2 \left( \tilde{\psi}_1 (1 + \sin^2(\gamma)) + \psi_4 n_1^2 + \psi_6 m_1^2 \right) \\
\sigma_{22} = 2 \left( \tilde{\psi}_1 + \psi_4 n_2^2 + \psi_6 m_2^2 \right) \\
\sigma_{33} = 2 \left( \tilde{\psi}_1 + \psi_4 n_3^2 + \psi_6 m_3^2 \right) \quad (C.57) \\
\tau_{12} = 2 \left( \tilde{\psi}_1 \sin^2(\gamma) + \psi_4 n_1 n_2 + \psi_6 m_1 m_2 \right) \\
\tau_{13} = \tau_{23} = 0
\]

where \(\alpha\) and \(\theta\) are the angle of the first and the second fiber, respectively, with respect the horizontal axis in the material configuration.

In the case of pure shear with volume preservation, there is a direct analytic solution and no optimization is required.

**Validation of Modified Anisotropic Constitutive Model**

To validate the constitutive model (see in sec.C.3), a simple unit cube has been simulated in Abaqus and compared with respect to the analytic solutions. Uniaxial, Biaxial, and Shear tests with different material properties and deformation ratios were tested. As an example, Figure C.5 shows a perfect matching between the analytic and simulation solutions for the following set of parameters,

- **Isotropic behavior:** \(D_1 = 0.05\) (kPa), \(D_2 = 5.0\) (-)
- **Anisotropic behavior:** \(k_1 = k_3 = 0.2\) (kPa), \(k_2 = k_4 = 3.0\) (-), \(\kappa_0 = 1000.0\)
- **Stretches in uniaxial/biaxial test:** \(\lambda = 0.5\), \(\mu = 0.5\)
- **Lateral displacement in shear test:** \(U_\tau = 0.5\)
- **Angle of fibers with respect to the horizontal axis in the material configuration:** \(\alpha = 0\), \(\theta = \pi/2\)

where \((D_1, D_2)\) are the material properties of the extracellular matrix, \((k_{1/3}, k_{2/4})\) defines the collagen fibers behavior, \(\kappa_0\) is the bulk modulus, \(\lambda, \mu\) are the horizontal and vertical stretches respectively, and \(U_\tau\) is the displacement applied to the mobile boundary in the pure shear test.

**C.5 Equivalence between Material Models**

An equivalence between the behavior of different hyperelastic material models can be point-wise established by studying the slope of the stress-stretch curves. Hereafter, we will refer to the initial slope of the stress-strain curve.
Let us consider a nearly-incompressible anisotropic hyperelastic material with two orthogonal families of fibers ($\psi(I_1, I_4, I_6)$). The Cauchy stress tensor reads as,

$$\sigma = -p\mathbf{1} + 2(\psi_1\bar{\mathbf{b}} + \psi_4\mathbf{N} + \psi_6\mathbf{M})$$  \hspace{1cm} (C.58)

where $\psi_1$, $\psi_4$, and $\psi_6$ are the derivatives of the SEF with respect to the modified first, and fourth invariants (e.g. $I_1 = J^{2/3}\tilde{I}_1$, equal when incompressibility is accounted for), $\mathbf{b} = J^{2/3}\tilde{\mathbf{b}}$ is the left Cauchy-Green tensor, $\mathbf{N} = \mathbf{n} \otimes \mathbf{n}$ is the spatial direction tensor of the first family of fibers ($\mathbf{n} = \mathbf{F}_n\mathbf{0} = (n_1, n_2, n_3)$), and $\mathbf{M} = \mathbf{m} \otimes \mathbf{m}$ is the spatial direction tensor of the second family of fibers ($\mathbf{m} = \mathbf{F}_m\mathbf{0} = (m_1, m_2, m_3)$).

Now, let us particularize to an uniaxial tensile test. After determining the hydrostatic pressure ($\sigma_{22} = 0$), the component of the Cauchy stress along the pulling axis ($\sigma_{11}$) is only a function of the stretch ($\lambda$). Hence, the derivative of $\sigma_{11}$ with respect to the stretch reads as,

$$\frac{\sigma_{11}(\lambda)}{\partial \lambda} = 2\left(\frac{\partial \psi_1}{\partial \lambda} I_1 (b_{11} - b_{22}) + \psi_1 \frac{\partial I_1}{\partial \lambda} (b_{11} - b_{22}) + \psi_1 I_1 \frac{\partial (b_{11} - b_{22})}{\partial \lambda}\right) + 2\left(\frac{\partial \psi_4}{\partial \lambda} (N_{11} - N_{22}) + \frac{\partial \psi_6}{\partial \lambda} (M_{11} - M_{22})\right)$$  \hspace{1cm} (C.59)
where the chain rule can be applied to the derivatives of the SEF ($\psi$) so as to derive them with respect to the invariants.

**Case of Application: Demiray-Holzapfel-Gasser-Ogden SEF**

Now let us consider an uniaxial tensile test with two families of in-plane orthogonal fibers as,

$$N = n \otimes n = \begin{bmatrix} \lambda^2 \cos^2 \theta & \sqrt{\lambda} \sin \theta \cos \theta & 0 \\ \sqrt{\lambda} \sin \theta \cos \theta & \frac{1}{\lambda} \sin^2 \theta & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$M = m \otimes m = \begin{bmatrix} \lambda^2 \sin^2 \theta & \sqrt{\lambda} \sin \theta \cos \theta & 0 \\ \sqrt{\lambda} \sin \theta \cos \theta & \frac{1}{\lambda} \cos^2 \theta & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

where $\theta$ is the angle formed between the first family of fibers ($n$) and the x-axis, and the second family of fibers ($m$) is orthogonal to the first family of fibers.

The invariants of a uniaxial tensile test reads as,

$$I_1 = tr(b) = \lambda^2 + \frac{2}{\lambda}$$

$$\frac{\partial I_1}{\partial \lambda} = 2\lambda - \frac{2}{\lambda^2}$$

$$I_4 = n_0 \cdot (Cn_0) = \lambda^2 \cos^2 \theta + \frac{1}{\lambda} \sin^2 \theta$$

$$\frac{\partial I_4}{\partial \lambda} = 2\lambda \cos^2 \theta - \frac{1}{\lambda^2} \sin^2 \theta$$

$$I_6 = \lambda^2 \sin^2 \theta + \frac{1}{\lambda} \cos^2 \theta$$

$$\frac{\partial I_6}{\partial \lambda} = 2\lambda \sin^2 \theta - \frac{1}{\lambda^2} \cos^2 \theta$$

Knowing that the SEF is composed of an isotropic hyperelastic defined by a Demiray SEF,$^{19}$ along with an anisotropic hyperelastic defined by a Holzapfel-Gasser-Ogden$^{20}$ is,

$$\psi = \tilde{\psi}_D(\tilde{C}) + \tilde{\psi}_{G0H}(\tilde{C})$$

$$\tilde{\psi}_D = D_1 \cdot (e^{D_2(I_1-3)} - 1)$$

$$\tilde{\psi}_{G0H} = \frac{k_1}{2 \cdot k_2} (e^{k_2(I_4-1)^2} - 1) + \frac{k_3}{2 \cdot k_4} (e^{k_4(I_6-1)^2} - 1)$$

Eventually, after some algebra and particularizing to the initial stretch ($\lambda = 1$), the
initial slope (i.e. initial equivalent Young modulus) reads as,

\[ \frac{\partial \sigma_{11}}{\partial \lambda} = 18D_1D_2 + 2k_1(3\cos^2\theta - 1)(1 + \cos^2\theta) + 2k_3(3\sin^2\theta - 1)(1 + \sin^2\theta) \]  

(C.62)

If the first family of fibers is aligned with the x-axis \( (\theta = 0) \),

\[ \frac{\partial \sigma_{11}}{\partial \lambda} = 18D_1D_2 + 8k_1 - 2k_3 \]  

(C.63)

If, in addition, both families of fibers present the same mechanical behavior \( (k_1 = k_3) \),

\[ \frac{\partial \sigma_{11}}{\partial \lambda} = 18D_1D_2 + 6k_1 \]  

(C.64)

Finally, if the isotropic contribution of the SEF is represented by a Neo-Hookean,

\[ \frac{\partial \sigma_{11}}{\partial \lambda} = 18C_{10} + 6k_1 \]  

(C.65)

and, then, we can force both material models to behave equivalently \( (C_{10} = D_1D_2) \), albeit this condition is only valid at the initial slope.
### Artificial Ray–Tracing in Optical Systems (ARiOS)

#### Chapter Contents

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When validating numerical simulations, to compare real experiments and numerical data, or simulations, is essential. However, clinical ophthalmic devices often provide with information that cannot be easily contrasted since the internal algorithms remain secret. Therefore, it is not a trivial task to find a common metric to compare, and validate, the numerical and experimental experiments. To tackle this lack of knowledge, a common measuring framework must be proposed and applied to both, simulations and clinical data.

The goal of the proposed ray-tracing algorithm (Artificial Ray-Tracing in Optical Systems, ARiOS) is to determine the optical features of the eye using only the geometry of the cornea. In this vein, only corneal topographies from clinic are needed to both, build patient-specific models for computational simulations, and obtain the visual quality by means of ray-tracing. Since the algorithm only relies in geometry, it can be applied to both geometries (clinical and numerical) in the same manner, allowing for a straightforward comparison. Otherwise, validating computational experiments with commercial devices would be hardly feasible.

The main features of the sofware are,

- Reading data from different sources (real topographers, and user-defined files).
- Constructing geometrical surfaces in the same reference framework (using Zernike polynomials, see in Sec. D.1).
- Fitting topographic data to a surface (see in Sections D.2).
- Obtaining its curvatures based on differential geometry (see in Section D.3).
- Performing the ray-tracing of the ocular system based on the 3-dimesional (3D) Snell’s vectorial law (see in Sec. D.4).
- Obtaining the aberrations of the system (see in Sec. D.5).

### D.1 Zernike Polynomials

Zernike polynomials are orthonormal polynomials over circular pupils. They are named after Fritz Zernike, due to his joined work with his PhD student Bernard Nijboer. Their success is associated to three main reasons:\(^1\)

- Their orthonomality over a circular pupil.
- Their relation with other classical aberrations (Seidel and Schwarzchild aberrations).
Their construction balances the high-order polynomials by lower-order polynomials so that the image intensity at the focal plane can be optimized when the amount of aberrations is low.

Furthermore, they have been widely applied in astronomy for atmospheric turbulence compensation,\(^2\) in vision for ocular aberration measurements,\(^3\) and in optical metrology for surface and transmitted wavefront representation.\(^4\)

Zernike polynomials are usually defined in polar coordinates \((\rho, \theta)\).\(^5\) \(\rho\) is the normalised radial coordinate \(\in [0, 1]\), and \(\theta\) is the azimuthal component \(\in [0, 2\pi]\).

Each Zernike polynomial (D.1) (see an extract in Fig. D.1) consist of a normalisation term \((N_m^n)\), a radial function \((R_m^n)\), and a triangular function \((\Theta_m)\). A double indexing scheme is used to describe the functions: \(n\) describes the highest power (order) of the radial polynomial \((R_m^n)\), and \(m\) describes the azimuthal frequency of the sinusoidal component.\(^6\)

\[
Z_m^n(\rho, \theta) = N_m^n \cdot R_m^n(\rho) \cdot \Theta_m \text{ with indices: } \begin{cases} 
  n \geq 0 \\
  n \geq m \\
  n - m \text{ even}
\end{cases} \quad (D.1)
\]

- Normalisation factor \((N_m^n)\)

\[
N_m^n = \sqrt{\frac{2(n + 1)}{1 + \delta_{m0}}} \quad (D.2)
\]

where \(\delta_{m0}\) is the Kronecker delta function \((\delta_{m0} = 0 \text{ if } m \neq 0). Otherwise, \(\delta_{m0} = 1)\).

- Radial function \((R_m^n)\)

\[
R_m^n(\rho) = \sum_{s=0}^{(n-|m|)/2} \frac{(-1)^s(n-s)!}{s!(n+|m|)/2-s|!(n-|m|)/2-s|!} \rho^{n-2s} \quad (D.3)
\]

- Triangular function \((\Theta_m)\)

\[
\Theta_m(\theta) = \begin{cases} 
  \cos|m|\theta & \text{if } m \geq 0 \\
  \sin|m|\theta & \text{if } m < 0
\end{cases} \quad (D.4)
\]

- Transformation between Single-Index and Double-Index notation

\[
\begin{cases} 
  n = \text{int}(\sqrt{2i+1}) + 0.5 - 1, \\
  m = 2i - n(n+2), \\
  i = \frac{n^2+2n+m}{2}
\end{cases} \quad (D.5)
\]

where \(\text{int}(x)\) stands for the largest integer smaller than \(x\), \((n, m)\) represent the double-index notation, and \(i\) represents the single-index notation.
When Zernike polynomials are used in optics, some of the coefficients are indicators of common pathologies such as astigmatism, or keratoconus (see in Table D.1). The most common are,

<table>
<thead>
<tr>
<th>(i)</th>
<th>(n)</th>
<th>(m)</th>
<th>Zernike Polynomials</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>Piston</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>-1</td>
<td>(2p \sin \theta)</td>
<td>Tilt</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>(2p \cos \theta)</td>
<td>Tip</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>-2</td>
<td>(\sqrt{6p^2} \sin 2\theta)</td>
<td>Oblique astigmatism</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
<td>(\sqrt{3}(2p^2 - 1))</td>
<td>Defocus</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>(\sqrt{6p^2} \cos 2\theta)</td>
<td>Vertical astigmatism</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>-1</td>
<td>(\sqrt{8}(3p^3 - 2p) \sin \theta)</td>
<td>Vertical coma</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1</td>
<td>(\sqrt{8}(3p^3 - 2p) \cos \theta)</td>
<td>Horizontal coma</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>-2</td>
<td>(\sqrt{10}(4p^4 - 3p^2) \sin 2\theta)</td>
<td>Secondary Oblique Astigmatism</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>0</td>
<td>(\sqrt{5}(6p^4 - 6p^2 + 1))</td>
<td>Primary spherical</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>2</td>
<td>(\sqrt{10}(4p^4 - 3p^2) \cos 2\theta)</td>
<td>Secondary Vertical Astigmatism</td>
</tr>
</tbody>
</table>

Table D.1: Zernike polynomials and their relation to optical aberrations.

Once Zernike polynomials are computed, a surface (e.g. Wavefront) can be represented as an infinite sum of terms,

\[
W(\rho = r/R_p, \theta) = \sum_{s=0}^{(n-|m|)/2} c^m_n \cdot Z^m_n(\rho, \theta)
\]

Figure D.1: Graphical representation of Zernike polynomials. Functions related with optical features (see in Table D.1) are highlighted (in red).
where \( R_p \) is the radius of the pupil under analysis (e.g., 3 mm), \( c_{mn} \) are the Zernike coefficients, and \( Z_{mn} \) the Zernike polynomials. Furthermore, the derivatives of the surface can be easily calculated using the chain rule,

\[
\frac{\partial W(\rho, \theta)}{\partial r} = \frac{\partial W(\rho, \theta)}{\partial \rho} \frac{\partial \rho}{\partial r} = \frac{\partial W(\rho, \theta)}{\partial \rho} \frac{1}{R} \\
\frac{\partial^2 W(\rho, \theta)}{\partial r^2} = \frac{\partial}{\partial r} \left( \frac{\partial W(\rho, \theta)}{\partial \rho} \right) \frac{1}{R} = \frac{\partial^2 W(\rho, \theta)}{\partial \rho^2} \frac{1}{R^2} \frac{\partial W(\rho, \theta)}{\partial \rho} \\
\frac{\partial^2 W(\rho, \theta)}{\partial r \partial \theta} = \frac{\partial^2 W(\rho, \theta)}{\partial \rho \partial \theta} \frac{1}{R}
\]

(D.7)

To perform a least-squares fitting of the Zernike coefficients to a certain surface data \( (S = (S_r, S_\theta, S_z)) \) in a polar coordinates \( (r, \theta, z) \), let us solve:

\[
c_{mn} = \text{pinv}(Z_m(S_r/R_p, S_\theta)) \cdot S_z
\]  

(D.8)

where \( c_{mn} \) is the vector of Zernike coefficients, \( Z_m(S_r, S_\theta) \) is the matrix of Zernike functions evaluated at the radial \( (S_r) \) and angular \( (S_\theta) \) coordinates of the surface \( (S) \), \( \text{pinv}(\bullet) \) is the pseudo-inverse of a rectangular matrix, and \( S_z \) is a vector containing the height (also elevation, sagitta) of the surface.
<table>
<thead>
<tr>
<th>index</th>
<th>n</th>
<th>m</th>
<th>$Z_n^m$</th>
<th>$(\mathcal{A}_n^m)_r$</th>
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Table D.2: 10-th Order Zernike polynomials and their Derivatives \((\partial Z, \partial^2 Z_{\theta\theta})\)

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<td>47</td>
<td>9</td>
<td>-5</td>
<td>$5r^5 \cos(50) \left( 36r^4 - 56r^2 + 21 \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>9</td>
<td>-3</td>
<td>$3r^3 \cos(30) \left( 84r^6 - 168r^4 + 105r^2 - 20 \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>9</td>
<td>-1</td>
<td>$\cos(\theta) \left( 126r^9 - 280r^7 + 210r^5 - 60r^3 + 5r \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>9</td>
<td>1</td>
<td>$-\sin(\theta) \left( 126r^9 - 280r^7 + 210r^5 - 60r^3 + 5r \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>9</td>
<td>3</td>
<td>$-3r^3 \sin(30) \left( 84r^6 - 168r^4 + 105r^2 - 20 \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>9</td>
<td>5</td>
<td>$-5r^5 \sin(50) \left( 36r^4 - 56r^2 + 21 \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>9</td>
<td>7</td>
<td>$-7r^7 \sin(70) \left( 9r^2 - 21 \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>9</td>
<td>9</td>
<td>$-9r^9\sin(9\theta)$</td>
<td>$-81r^7\cos(9\theta)$</td>
<td>$-81r^8\sin(9\theta)$</td>
</tr>
<tr>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----------------------</td>
<td>----------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>55</td>
<td>10</td>
<td>-10</td>
<td>$10r^{10}\cos(10\theta)$</td>
<td>$-100r^{10}\sin(10\theta)$</td>
<td>$100r^8\cos(10\theta)$</td>
</tr>
<tr>
<td>56</td>
<td>10</td>
<td>-8</td>
<td>$8r^8\cos(8\theta)\left(10r^2 - 9\right)$</td>
<td>$-64r^8\sin(8\theta)\left(10r^2 - 9\right)$</td>
<td>$32r^7\cos(8\theta)\left(25r^2 - 18\right)$</td>
</tr>
<tr>
<td>57</td>
<td>10</td>
<td>-6</td>
<td>$6r^6\cos(6\theta)\left(45r^4 - 72r^2 + 28\right)$</td>
<td>$-36r^6\sin(6\theta)\left(45r^4 - 72r^2 + 28\right)$</td>
<td>$36r^5\cos(6\theta)\left(75r^4 - 96r^2 + 28\right)$</td>
</tr>
<tr>
<td>58</td>
<td>10</td>
<td>-4</td>
<td>$4r^4\cos(4\theta)\left(120r^6 - 252r^4 + 168r^2 - 35\right)$</td>
<td>$-16r^4\sin(4\theta)\left(120r^6 - 252r^4 + 168r^2 - 35\right)$</td>
<td>$16r^3\cos(4\theta)\left(300r^6 - 504r^4 + 252r^2 - 35\right)$</td>
</tr>
<tr>
<td>59</td>
<td>10</td>
<td>-2</td>
<td>$2r^2\cos(2\theta)\left(210r^8 - 504r^6 + 420r^4 - 140r^2 + 15\right)$</td>
<td>$-4r^2\sin(2\theta)\left(210r^8 - 504r^6 + 420r^4 - 140r^2 + 15\right)$</td>
<td>$4r\cos(2\theta)\left(1050r^8 - 2016r^6 + 1260r^4 - 280r^2 + 15\right)$</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>0</td>
<td>$0$</td>
<td>$0$</td>
<td>$0$</td>
</tr>
<tr>
<td>61</td>
<td>10</td>
<td>2</td>
<td>$-2r^2\sin(2\theta)\left(210r^8 - 504r^6 + 420r^4 - 140r^2 + 15\right)$</td>
<td>$-4r^2\sin(2\theta)\left(210r^8 - 504r^6 + 420r^4 - 140r^2 + 15\right)$</td>
<td>$-4r^2\sin(2\theta)\left(1050r^8 - 2016r^6 + 1260r^4 - 280r^2 + 15\right)$</td>
</tr>
<tr>
<td>62</td>
<td>10</td>
<td>4</td>
<td>$-4r^4\sin(4\theta)\left(120r^6 - 252r^4 + 168r^2 - 35\right)$</td>
<td>$-16r^4\sin(4\theta)\left(120r^6 - 252r^4 + 168r^2 - 35\right)$</td>
<td>$-16r^4\sin(4\theta)\left(300r^6 - 504r^4 + 252r^2 - 35\right)$</td>
</tr>
<tr>
<td>63</td>
<td>10</td>
<td>6</td>
<td>$-6r^6\sin(6\theta)\left(45r^4 - 72r^2 + 28\right)$</td>
<td>$-36r^6\sin(6\theta)\left(45r^4 - 72r^2 + 28\right)$</td>
<td>$-36r^5\sin(6\theta)\left(75r^4 - 96r^2 + 28\right)$</td>
</tr>
<tr>
<td>64</td>
<td>10</td>
<td>8</td>
<td>$-8r^8\sin(8\theta)\left(10r^2 - 9\right)$</td>
<td>$-64r^8\cos(8\theta)\left(10r^2 - 9\right)$</td>
<td>$-32r^7\sin(8\theta)\left(25r^2 - 18\right)$</td>
</tr>
<tr>
<td>65</td>
<td>10</td>
<td>10</td>
<td>$-10r^{10}\cos(10\theta)$</td>
<td>$-100r^{10}\cos(10\theta)$</td>
<td>$-100r^9\sin(10\theta)$</td>
</tr>
</tbody>
</table>

Table D.3: 10-th Order Derivatives of Zernike Polynomials (cont.). $(\partial Z_{\theta}, \partial^2 Z_{\theta}, \partial^2 Z_{\theta})$
D.2 Second Order Surfaces

Occasionally, the optical elements of the eye can be approximated rather precisely using a second order surface. Of course, the patient-specific information is lost, but in theory it should preserve key factors such as the astigmatic axes, or a good approximation of the corneal curvature. However, when the shape of the cornea greatly diverges from the average (also, normal or healthy) shape, these approaches will not remain valid.

**Sphere**

\[
(x - x_c)^2 + (y - y_c)^2 + (z - z_c)^2 = R^2
\]  
(D.9)

where \((x_c, y_c, z_c) [m]\) is the offset (center) of the surface, and \(R [m]\) is the radius of curvature of the surface.

**General Biconic**

This surface has been proposed previously as the optimal to approach a healthy average cornea.\(^7\) Furthermore, several particular cases can be derived from this general expression (D.10): ellipsoid of revolution, and torus.

\[
z = z_c + \frac{c_x(x - x_c)^2 + c_y(y - y_c)^2}{1 + \sqrt{1 - (1 + Q_x)c_x^2(x - x_c)^2 - (1 + Q_y)c_y^2(y - y_c)^2}}
\]  
(D.10)

where \((x_c, y_c, z_c) [m]\) is the offset of the surface, \(c_x (1 / R_x)\), and \(c_y (1 / R_y) [m^{-1}]\) are the curvatures in \(x-, y-\) direction, and \(Q_x\) and \(Q_y\) are the asphericities in \(x-, y-\) direction. Two particular shapes are obtained as a particularization of the general biconic: the ellipsoid of revolution \((c_x = c_y = c, Q_x = Q_y)\), and the torus \((c_x \neq c_y = c, Q_x = Q_y = 0)\).

**Quadric**

The most general expression of a quadric surface has into account additional rotations,

\[
A \cdot x^2 + B \cdot y^2 + C \cdot z^2 + D \cdot xy + E \cdot xz + F \cdot yz + G \cdot x + H \cdot y + I \cdot z = 1
\]  
(D.11)

where \((A, B, C, D, E, F, G, H, I)\) are the coefficients of the quadric. In matrix notation, let \(\mathbf{M}\) be the matrix of the second order coefficients, and \(\mathbf{P}\) the vector of linear
coefficients,

\[
M = \begin{bmatrix}
A & D/2 & E/2 \\
D/2 & B & F/2 \\
E/2 & F/2 & C
\end{bmatrix}
\]

\[
P = \begin{bmatrix}
G/2 \\
H/2 \\
I/2
\end{bmatrix}
\]

then define the problem definition is,

\[
x^T M x + 2 P^T x + c = 0, \quad (D.12)
\]

where \( x \) is the surface coordinates vector, and \( c \) is a scalar constant.

The fitting problem can be solved by least-squares as,

\[
\begin{bmatrix}
x_1^2 & y_1^2 & z_1^2 & x_1 y_1 & x_1 z_1 & y_1 z_1 & x_1 & y_1 & z_1 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
x_n^2 & y_n^2 & z_n^2 & x_n y_n & x_n z_n & y_n z_n & x_n & y_n & z_n
\end{bmatrix}_{(n \times 9)}
\begin{bmatrix}
A \\
B \\
C \\
D \\
E \\
F \\
G \\
H \\
I
\end{bmatrix} = \mathbf{1}_{(n \times 1)} \rightarrow \mathbf{xc} = \mathbf{1}
\]

inverting the system, the vector of coefficients (\( \tilde{c} \)) arises,

\[
\tilde{c} = pinv(\mathbf{X})\mathbf{1} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T
\]

where \( \mathbf{X} \) is the rectangular matrix of coordinates, and the \( pinv(\cdot) \) operator is the pseudo-inverse of a rectangular matrix.

### D.3 Differential Geometry of Surfaces: Curvature

**Fundamental Forms**

Let \( S(u, v) \) be a parametric smooth surface in the three dimensional Euclidean space (\( \mathbb{R}^3 \)), continue and differentiable. Let \( \partial S_u \) and \( \partial S_v \) be the partial derivatives of \( S \) on \( u \) and \( v \). Finally, let \( \tilde{x} \) be a vector defining a point on the parametric surface, \( S(u, v) \).

\[
\tilde{x} = \{ u, v, S(u, v) \}
\]

(D.14)
The First fundamental form (I) of the parametric surface is,\(^8\)

\[
I = \begin{bmatrix} E & F \\ F & G \end{bmatrix}
\]

where E, F, and G, are defined by the inner product \(\langle \cdot \rangle\) as,

\[
E = \langle \partial_{\tilde{x},u}, \partial_{\tilde{x},u} \rangle = \partial_{\tilde{x},u} \cdot \partial_{\tilde{x},u}
\]

\[
F = \langle \partial_{\tilde{x},u}, \partial_{\tilde{x},v} \rangle = \partial_{\tilde{x},u} \cdot \partial_{\tilde{x},v}
\]

\[
G = \langle \partial_{\tilde{x},v}, \partial_{\tilde{x},v} \rangle = \partial_{\tilde{x},v} \cdot \partial_{\tilde{x},v}
\]

(D.15)

where \(\partial_{\tilde{x},u}\) is the partial derivative of \(\tilde{x}\) with respect \(u\), and \(\partial_{\tilde{x},v}\) is the partial derivative of \(\tilde{x}\) with respect \(v\).

The Second fundamental form (II) of the parametric surface is,

\[
II = \begin{bmatrix} L & M \\ M & N \end{bmatrix}
\]

where L, M, N are defined as,

\[
L = \langle \partial^2_{\tilde{x},uu}, \tilde{n} \rangle = \partial^2_{\tilde{x},uu} \cdot \tilde{n}
\]

\[
M = \langle \partial^2_{\tilde{x},uv}, \tilde{n} \rangle = \partial^2_{\tilde{x},uv} \cdot \tilde{n}
\]

\[
N = \langle \partial^2_{\tilde{x},vv}, \tilde{n} \rangle = \partial^2_{\tilde{x},vv} \cdot \tilde{n}
\]

(D.16)

where \(\partial_{\tilde{x},uu}\), \(\partial_{\tilde{x},uv}\), and \(\partial_{\tilde{x},vv}\) are the second partial derivatives of \(\tilde{x}\) with respect \(u\), and \(v\). Finally, \(\tilde{n}\) is the normal vector to the parametric surface\(^9\) defined as,

\[
\tilde{n} = \frac{\partial_{\tilde{x},u} \times \partial_{\tilde{x},v}}{|\partial_{\tilde{x},u} \times \partial_{\tilde{x},v}|}
\]

(D.17)

Particularizing to polar coordinates (\(\tilde{x} = \{r, \theta, S(r, \theta)\}\)), the derivatives become,

\[
\partial_{\tilde{x},r} = \{\cos \theta, \sin \theta, \partial S,_{r}\}
\]

\[
\partial_{\tilde{x},\theta} = \{-r \sin \theta, r \cos \theta, \partial S,_{\theta}\}
\]

\[
\partial^2_{\tilde{x},rr} = \{0, 0, \partial^2 S,_{rr}\}
\]

\[
\partial^2_{\tilde{x},\theta\theta} = \{-r \cos \theta, -r \sin \theta, \partial^2 S,_{\theta\theta}\}
\]

\[
\partial^2_{\tilde{x},r\theta} = \{-\sin \theta, -\cos \theta, \partial^2 S,_{r\theta}\}
\]

(D.18)

the First fundamental form,

\[
E = 1 + \partial^2 S,_{r}
\]

\[
F = \partial S,_{r} \partial S,_{\theta}
\]

\[
G = r^2 + \partial^2 S,_{\theta}
\]

(D.19)
and the Second fundamental form,

\[
\begin{align*}
L &= \frac{\det(\partial^2 S_{,rr}) \partial S_{,r} \partial S_{,\theta})}{\sqrt{EG - F^2}} \\
M &= \frac{\det(\partial^2 S_{,r\theta}) \partial S_{,r} \partial S_{,\theta})}{\sqrt{EG - F^2}} \\
N &= \frac{\det(\partial^2 S_{,\theta\theta}) \partial S_{,r} \partial S_{,\theta})}{\sqrt{EG - F^2}}
\end{align*}
\] (D.20)

**Curvatures of a Parametric Surface based on its Fundamental Forms**

Using the first and second fundamental forms, the curvatures of the parametric surface \( S \) can be derived.\(^{10}\)

**Gaussian, Mean and Principal Curvatures**

Gaussian curvature, \( K \), only depends on how the distances are measured on the surface. Therefore, it is an intrinsic property of the surface. Its definition is given by the product of the principal curvatures \( \kappa_1, \kappa_2 \),

\[
K = \kappa_1 \kappa_2 = \frac{LN - M^2}{EG - F^2}
\] (D.21)

Contrarily, Mean curvature, \( H \), is the average of the principal curvature and, therefore, an extrinsic property of the surface,

\[
H = \frac{\kappa_1 + \kappa_2}{2} = \frac{EN + GL - 2FM}{2(EG - F^2)}
\] (D.22)

Hence, the principal curvatures \( \kappa_1 = \kappa_{\text{max}}, \kappa_2 = \kappa_{\text{min}} \) can be derived from the Gaussian and Mean curvature as,

\[
\begin{align*}
\kappa_1 &= \kappa_{\text{max}} = H + \sqrt{H^2 - K} \\
\kappa_2 &= \kappa_{\text{min}} = H - \sqrt{H^2 - K}
\end{align*}
\] (D.23)

and the principal directions can be derived by solving a quadratic equation in \( \lambda \)

\[
(FN - GM)\lambda^2 + (EN - GL)\lambda + (EM - FL) = 0
\] (D.24)

where the coefficients of the quadratic equation become all zero when the principal directions are not defined (umbilical point). When the point in the surface is non-umbilical, there are always two orthogonal principal directions.
Axial and Instantaneous Curvature

Assuming symmetry of revolution, all the angular derivatives are set to zero \( \partial^2 S_{r(\theta)} = \partial^2 S_{r(\theta)} = 0 \). Then, the principal curvatures reduce to,

\[
\tilde{\kappa}_1 = \frac{\partial S_{r(r)}}{r(1 + \partial^2 S_{r(r)})^{1/2}} \\
\tilde{\kappa}_2 = \frac{\partial^2 S_{r(rr)}}{(1 + \partial^2 S_{r(r)})^{3/2}}
\]  \( \text{(D.25)} \)

And taking the inverse of the curvatures, the Sagittal (axial) radius \( R_S \) and the Tangential (Instantaneous) radius \( R_T \) arise,\(^{11} \)

\[
R_S = \frac{r(1 + \partial^2 S_{r(r)})^{1/2}}{\partial S_{r(r)}} \\
R_T = \frac{(1 + \partial^2 S_{r(r)})^{3/2}}{\partial^2 S_{r(rr)}}
\]  \( \text{(D.26)} \)

D.4 Ray–Tracing in Optical Systems

Geometrical ray-tracing algorithms compute the geometrical path of a bundle (or pencil) of light rays crossing the optical system. When one of the rays reaches a surface (lens), and the index of refraction is different with respect the previous medium, the physical interaction of the light in the interface of the media (refraction and reflection) is determined by means of the 3D Snell’s Law. Currently, our algorithm has different assumptions such as: the light is propagated in a straight-line path since the medium possess an homogeneous (isotropic) index of refraction, the diffusion in the surface or the medium is not accounted, and the optical system is diffraction limited. The last assumption is of special importance since it will determine whether the geometrical approach is valid, or the physical approach should be taken. As a thumb rule, the Rayleigh limit says that if the wave aberration is less than one quarter of the wave length, the system can be regarded as diffraction limited. Equivalently, a system is diffraction limited if the peak-to-valley value of the wave aberration is smaller than \( \lambda / 4 \).\(^{12} \) In practice, due to the range of pupil diameters when the eye is explored (3 to 4 mm in radius), we will assume that the geometrical approach is valid.

3D Snell’s Vectorial Law

Snell’s law (D.27) allows describing the behavior of the incident light on an optical surface, which separates two physical media of different refractive index (see in
Figure. D.2).\textsuperscript{13}

\[
\begin{align*}
\delta &= \frac{n_1}{n_2} \\
\theta_1 &= \frac{\arccos(-\hat{i} \cdot \hat{n})}{|\hat{i}|} \\
\hat{i} &= \delta \hat{n} \times (-\hat{n} \times \hat{i}) - \hat{n} \sqrt{1 - \delta^2 (\hat{n} \times \hat{i}) \cdot (\hat{n} \times \hat{i})} \\
\hat{r} &= \hat{i} + 2 \cos(\theta_1) \hat{n} \\
\theta_2 &= \frac{\arccos(-\hat{r} \cdot \hat{n})}{|\hat{r}|} \\
\end{align*}
\]

where the sub-index 1 denotes the first medium (in-going light), the sub-index 2 denotes the second medium (out-going light), \( n_1 \) and \( n_2 \) are the refractive indices of the first and second medium respectively, \( \theta_1 \) is the incidence angle, \( \theta_2 \) is the refraction (transmission) angle, \( (\hat{i}, \hat{r}, \hat{n}) \) are the incident, refracted (transmitted) and reflected rays, and \( \hat{n} \) is the normal to the optical surface in the point of evaluation.

**Basic Grounds in Optical Systems, and Navarro’s Schematic Eye Model**

When using geometric optics, many different concepts are used to analyse an optical system.\textsuperscript{14} These can be physical elements that block, refract, reflect, and absorb the light, or a mathematical entelechy that serves to solve the problem properly. Besides, they separate the **Object Space** (space where the actual object lies) from the **Image Space** (space where the object is formed). However, when the concept of optical system is applied to ophthalmology, not all of them are longer required,

- **Lenses.** All elements that reflects and refracts the light along the system, including the cornea, the crystalline lens, or artificial lenses introduced clinically. Besides, diffusive effects in the surface can occur. However, regarding geometrical ray-tracing in ophthalmic practice, we will focus only in refraction. In the eye, cornea and crystalline are lenses. Retina acts as the final surface of the optical system, where the image is formed.

- **Aperture Stop.** Normally, is defined as the diaphragm of the system that allows passing the cone of light. It limits the amount of light passing into the image space, and, therefore, how well-defined is the object perceived. Regarding ophthalmology, the iris will act as diaphragm.

- **Chief Ray.** By definition, it is the ray that emerges from the outest off-axis object point \((P)\), and crosses at the center of the Aperture Stop \((AS)\). To calculate it,
it is necessary to solve an optimization process that looks for the unknown ray that, after crossing some optical elements, will hit the Aperture Stop in the center (see in Figure D.3).

**Figure D.3: Definition of Chief Ray in the Human Eye.** An optimization procedure is used to look for the ray that will hit the center of the Aperture Stop, after crossing the precedent optical elements. Shaded red area corresponds to all the tested combinations, whereas the solid red line corresponds to the final Chief ray. The intersection between the prolongation of the incident Chief ray (dashed red line) with the optical axis will determine the center of the Entrance Pupil (EnP). The intersection between the prolongation of the emerging Chief ray (dashed red line) and the optical axis will determine the center of the Exit Pupil.

**Marginal Rays.** By definition, all the rays emerging from an on-axis object point, and grazing the outer rim of the Aperture Stop are marginal rays. To calculate them, it is also necessary an optimization procedure that looks for the rays that will impact in the edge of the Aperture Stop, after crossing all the optical elements before it (see in Figure D.4).

**Figure D.4: Definition of Marginal Rays in the Human Eye.** An optimization procedure is used to look for the rays that will graze the outer rim of the Aperture Stop, after crossing the precedent optical elements. Shaded red area corresponds to all the tested combinations, whereas the solid red line corresponds to the final Marginal ray. The intersection between the prolongation of the Marginal rays and the plane of the Entrance and Exit pupil will determine the diameters of the Entrance and Exit Pupils (maximum cone of light ingoing in the system).

**Entrance and Exit Pupils.** They are the (virtual) entrance and exit pupils of the optical system. In summary, they represent the image of the Aperture Stop (AS) of the system, when observed through all the elements before the AS (Entrance Pupil), or when observed only through the elements after the AS (Exit Pupil).
They can be obtained by means of ray-tracing (see in Figures D.3 and D.4).\(^{15}\)

In the eye, the Exit Pupil is almost coincident with the plane of the physical iris, whereas the Entrance Pupil is slightly before and magnified about a 13%.\(^{16}\)

Besides, when the optical system under consideration is the human eye, several axes can be distinguished (see in Figure D.5, right panel): visual axis, optical axis, line of sight, and pupillary axis. Physiologically, the eye rotates to align the visual axis with the object. Usually, these axes are slightly rotated with respect to the optical axis (around 5 to 7°). In our case, and for the sake of simplicity, the optical axis is considered when computing on-axis ray-tracing.

To represent the most common aberrations in the human eye, schematic models can be used. Among all, Navarro’s Schematic Eye Model is chosen.\(^{17}\) This model can be used to describe accommodation, chromatic dispersion, and spherical aberration as a function of the iris diameter with a good accuracy. All the surfaces in the model are represented by biconics (D.10). The main distances (gathered in Table D.4) depend in the level of accommodation of the system (D.28).

<table>
<thead>
<tr>
<th>Surface</th>
<th>(r_c)</th>
<th>(L)</th>
<th>(n)</th>
<th>(Q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal frontal surface</td>
<td>7.72</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cornea</td>
<td>-</td>
<td>0.55</td>
<td>1.3670</td>
<td>-0.26</td>
</tr>
<tr>
<td>Corneal back surface</td>
<td>6.50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anterior Chamber</td>
<td>-</td>
<td>3.05 - (L_2)</td>
<td>1.3374</td>
<td>0</td>
</tr>
<tr>
<td>Front surface of eye lens</td>
<td>10.20 - (r_{C3})</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eye Lens</td>
<td>-</td>
<td>4.00 + (L_3)</td>
<td>1.42 + (n_3)</td>
<td>-3.1316 - (Q_3)</td>
</tr>
<tr>
<td>Back surface of eye lens</td>
<td>-6.00 + (r_{C4})</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vitreous</td>
<td>-</td>
<td>16.403</td>
<td>1.3360</td>
<td>-1.00 - (Q_4)</td>
</tr>
</tbody>
</table>

Table Legend and Units. \(r_c\) [mm] is the radius of curvature of the surface; \(L\) [mm] is the length of the medium; \(n\) is the refractive index of the medium without chromatic dispersion; \(Q\) is the asphericity of the surface; \(L_2, L_3, n_3, Q_3, Q_4, r_{C3},\) and \(r_{C4}\) are variable distances that depend on the level of accommodation (a) of the system (D.28).

\[
\begin{align*}
r_{C3} &= 1.75n(A + 1), \\
r_{C4} &= 0.2294ln(A + 1), \\
L_2 &= 0.05ln(A + 1), \\
L_3 &= 0.1ln(A + 1), \\
n_3 &= 9e^{-5}(10A + A^2), \\
Q_3 &= 0.34ln(A + 1), \\
Q_4 &= 0.125ln(A + 1).
\end{align*}
\]

where A is the state of accommodation in dioptres (d).

Under relaxation conditions (far sight), the main dimensions of the schematic eye are computed using an accommodation (a) of 0 dioptres (see Figure D.5 and Table D.5).
To include the dispersion of the eye, the Herzberger equations (D.29) are used,

\[
n(\lambda) = a_1(\lambda)n^{**}(\lambda = 365\,nm) + a_2(\lambda)n_F(\lambda = 486.1\,nm) + a_3(\lambda)n_c(\lambda = 656.3\,nm) + a_4(\lambda)n^*(\lambda = 1014\,nm)
\]

\[
a_1(\lambda) = 0.66147196 - 0.40352796\lambda^2 + \frac{0.2804679}{\lambda^2 - \lambda_0^2} + \frac{0.03385979}{(\lambda^2 - \lambda_0^2)^2}
\]

\[
a_2(\lambda) = -4.20146383 + 2.73508956\lambda^2 + \frac{1.50543784}{\lambda^2 - \lambda_0^2} - \frac{0.11593235}{(\lambda^2 - \lambda_0^2)^2}
\]

\[
a_3(\lambda) = 6.29834237 - 4.69409935\lambda^2 - \frac{1.5750865}{\lambda^2 - \lambda_0^2} + \frac{0.10293038}{(\lambda^2 - \lambda_0^2)^2}
\]

\[
a_4(\lambda) = -1.75835059 + 2.36253794\lambda^2 + \frac{0.35011657}{\lambda^2 - \lambda_0^2} - \frac{0.02085782}{(\lambda^2 - \lambda_0^2)^2}
\]

where \(\lambda\) is the wavelength of light in micrometers, \(\lambda_0^2\) is a constant (0.028 \(\mu m^2\)), and \(n^{**}, n_F, n_c, n^*\) are the refractive indices of the ocular media (see in Table D.6).

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where \(\lambda\) is the wavelength of light in micrometers, \(\lambda_0^2\) is a constant (0.028 \(\mu m^2\)), and \(n^{**}, n_F, n_c, n^*\) are the refractive indices of the ocular media (see in Table D.6).
Mathematical Assets: Geometrical Intersections

Apart from the 3D Snell’s law, one of the main mathematical problems to solve in ray-tracing is to compute the intersection between rays and lenses. Usually, in a general problem, an optimization process is needed. This section gathers how to compute the intersection of lines (or vectors) with planes, spheres, and general surfaces.

**Line to Line Intersection**

Let \( r \) and \( s \) be two straight lines whose vectorial parametric expressions are,

\[
\begin{align*}
    r &= O_r + \lambda t_r \\
    s &= O_s + \mu t_s
\end{align*}
\]

where \( O_{r/s} \) are the origin points, \( \lambda, \mu \) are the parametric constants, and \( t_{r/s} \) are the direction vectors of the lines.

The intersection point \( p \) between both lines, if exists, must fulfill the relation \( r(p) = s(p) \). When the lines are defined in the 3-dimensional Euclidean space (\( \mathbb{R}^3 \)), it is unlikely that an intersection exists, as the lines will probably cross. Then, the objective is to find the set of parametric constants \((\lambda, \mu)\) that minimizes the distance between lines,

\[
f = \sum ||r - s||^2
\]

\[
f = \sum ||O_r + \lambda t_r - (O_s + \mu t_s)||^2
\]

\[
\arg\min_{\lambda,\mu} f(\lambda, \mu) = 0
\]

(D.31)

After the minimization, if a solution exists, the difference between both lines tends to zero, and the intersection point \((p)\) is given evaluating any of the intersecting lines \((p = r(\lambda) = s(\mu))\). Otherwise, the solution does not exist.

**Line to Plane Intersection**

Let \( r \) and \( \Pi_Q \) be a straight line and a randomly oriented plane respectively, both defined in \( \mathbb{R}^3 \), and whose parametric expressions are,

\[
\begin{align*}
    r &= O_r + \lambda t_r \\
    \Pi_Q &= q_0 + (q_1 - q_0)u + (q_2 - q_0)v
\end{align*}
\]

(D.32)
where $O_r$ is the origin point, $\lambda$ is the parametric constant, and $t_r$ is the direction vector of $r$; $q_{0/1/2}$ are three co-planar points contained in $\Pi_Q$, and $u, v$ are the parametric constants.

The intersection of the line with the plane is given by the linear system, $c = V \cdot p_0$, or, equivalently in matrix notation,

$$
\begin{bmatrix}
\lambda \\
u \\
v
\end{bmatrix} =
\begin{bmatrix}
-t_1^r & q_1^0 - q_1^0 & q_1^2 - q_1^0 \\
-t_2^r & q_2^0 - q_2^0 & q_2^2 - q_2^0 \\
-t_3^r & q_3^0 - q_3^0 & q_3^2 - q_3^0
\end{bmatrix} \cdot
\begin{bmatrix}
O_r^0 - q_1^0 \\
O_r^0 - q_2^0 \\
O_r^0 - q_3^0
\end{bmatrix}
$$

where $c$ is a 3x1 vector containing the parametric constants, $V$ is a 3x3 matrix formed by the direction vector of the line ($t_r$), and the co-planar vectors of the plane $(q_1 - q_0$ and $q_2 - q_0)$, and $p_0$ is a 3x1 vector containing the difference between the origin points of the line and the plane ($O_r - q_0$).

Once the parametric constants are obtained, the intersection point is given by $r(\lambda)$ or $\Pi_Q(u, v)$, independently. When $(u, v) \in [0, 1]$, and $(u + v) \leq 1$, the intersection point is within the triangle spanned by $(q_0, q_1, q_2)$.

**Line to Sphere Intersection**

Let $r$ and $S$ be a straight line and a randomly oriented sphere respectively, both defined in $\mathbb{R}^3$, and whose equations are,

$$
r = O_r + \lambda t_r
$$

$$
S = ||x_s - c_s||^2 = (x - x_0)^2 + (y - y_0)^2 + (z - z_0)^2 = R_S^2
$$

where $O_r$ is the origin point, $\lambda$ is the parametric constant, and $t_r$ is the direction vector of $r$; $x_s$ is a vector defining the coordinates $(x, y, z)$ of a point contained in the surface of the sphere, $c_s$ is a vector defining the center $(x_0, y_0, z_0)$ of the sphere, and $R_S$ is the radius of the sphere.

To solve analytically the intersection, let assume that the intersection point is $p = r$. Evaluating in the sphere ($S(p)$) and developing the equations, a second-order function of the parametric constant $\lambda$ is obtained,

$$
f(\lambda) = C_1 \lambda^2 + C_2 \lambda + C_3
$$

$$
C_1 = t_r \cdot t_r
$$

$$
C_2 = 2t_r \cdot (O_r - c_s)
$$

$$
C_3 = (O_r - c_s) \cdot (O_r - c_s) - R_S^2
$$

Obtaining the roots of the second-order equation, two feasible solutions are obtained. Hence, evaluating $r(\lambda_i), i = 1, 2$ will lead to different scenarios,
• \( r(\lambda_1), r(\lambda_2) \in \mathbb{C}^3 \), there is no intersection.

• \( r(\lambda_1) \neq r(\lambda_2) \in \mathbb{R}^3 \), there are 2 intersection points (line through the sphere).

• \( r(\lambda_1) = r(\lambda_2) \in \mathbb{R}^3 \), there is 1 intersection point (line tangent to the sphere).

**Line to General Surface**

Generalizing, a line-surface intersection problem can be regarded as the search of the optimal \( p \) that fulfills the relation \( r(p) - S(p) = 0 \), where \( r \) defines a straight line and \( S \) a general infinite surface in the Euclidean space \((\mathbb{R}^3)\). Although when the surfaces are sufficiently simple this problem can be solved analytically (i.e. sphere or plane), in general an optimization process is required.

\[
    f = \sum ||r(x(\lambda), y(\lambda), z(\lambda)) - S(x(\lambda), y(\lambda), z(\lambda))||^2 \\
    f = \sum ||O_r + \lambda t_r - S||^2 \\
    \arg\min_\lambda f(\lambda) = 0
\]  

(D.35)

Furthermore, if the definition of the surface is carried out in polar coordinates, the line must be expressed also in polar coordinates to solve the problem (e.g. the case of a Zernike surface). Knowing that the relation between Cartesian and Polar coordinates is given by,

\[
    \rho = \sqrt{x^2 + y^2} \\
    \theta = \arctan\left(\frac{y}{x}\right) \\
    z = z
\]

(D.36)

the relation between parametric equations in both coordinates systems is given by,

\[
    \begin{bmatrix}
        r_\rho \\
        r_\theta \\
        r_z
    \end{bmatrix} = \begin{bmatrix}
        \sqrt{(O'_{1} + \lambda t'_{1})^2 + (O'_{2} + \lambda t'_{2})^2} \\
        \arctan\left(\frac{O'_z + \lambda t'_z}{O'_{1} + \lambda t'_{1}}\right) \\
        O'_z + \lambda t'_z
    \end{bmatrix}
\]

Hence, the optimization problem tries to minimize the difference \( r(p) - S(p) = 0 \) for the parametric constant \( \lambda \) in polar coordinates,

\[
    g = \sum ||r(\rho(\lambda), \theta(\lambda), z(\lambda)) - S(\rho(\lambda), \theta(\lambda), z(\lambda))||^2 \\
    \arg\min_\lambda g(\lambda) = 0
\]

(D.37)

Once the parametric constant \( \lambda \) is obtained, the intersection point is given by evaluating the parametric equation of the line.
Spatial Constraints for Finite Surfaces (3D Patches)

When the surface is assumed to be ‘infinite’, no constrains are needed in the optimization process. The line will always intersect the surface in a point, but when it is parallel to it. However, if the surface is ‘finite’ (i.e. a patch), the line will not intersect the surface when is not aiming at it (see points $P$ and $Q$ in Figure D.6, left panel). Then, it is critical to provide the correct constraints over the parametric constant ($\lambda$) to find a solution. The approach to tackle this problem is two-fold: to check if the line aims to the patch, and, then, to compute the constraints in $\lambda$.

First, it is necessary to know the limits of the solid angles (i.e. cone of sight) within where the solution is feasible (see azimuth $\phi$ and inclination $\theta$ in Figure D.6, right panels). To compute the solid angles of the patch with respect to the origin point of the line ($O_r$), a spherical coordinate system is used,

\[
\rho = \sqrt{x^2 + y^2 + z^2} \\
\theta = \arccos\left(\frac{z}{\rho}\right) \\
\phi = \arctan\left(\frac{y}{x}\right)
\]  

where $\theta \in [0, 180^\circ]$ is the inclination, $\phi \in [0, 360^\circ]$ is the azimuth, and $\rho \geq 0$ is the radius.

For all the points in the periphery of the patch ($p_i \in \Omega_S$), the direction vectors ($t_{p_i}$) with respect to the origin of the line ($O_r$) are computed as $t_{p_i} = p_i - O_r$. Afterwards, the direction vectors ($t_{p_i}(x, y, z)$) are transformed to Spherical coordinates ($t_{p_i}(\rho, \theta, \phi)$), and the extreme values in $\phi$ and $\theta$ angular directions are taken to compute the sets of constraints ($\bar{\phi}, \bar{\theta} = \{\min(t_{p_i})_{\phi, \theta}, \max(t_{p_i})_{\phi, \theta}\}$). If the point lies within the limits of the patch (i.e. the $O_r \in \Omega_S$), the angular constrains are given by $\bar{\phi} \in [0, \max(t_{p_i})_{\phi}]$, $\bar{\theta} \in [-\pi, \pi]$. If, and only if, the angles of the line direction ($t_r(\rho, \theta, \phi)$) range in the limits of the angular constrains, the line is likely to intersect the patch (i.e. the line aims at the 3D patch).

Second, assuming that the origin of the line lies outside the periphery of the patch ($O_r \notin \Omega_S$), only intersection points ($p$) inside the patch will be valid (see in Figure D.7). All intersection points whose distance with respect to the center of the patch are greater than the radius of the patch are out of bounds ($\rho(\lambda) > R_S$). Now, let us assume that there exists a feasible intersection point ($p$) so that $r(p) - S(p) = 0$, then its distance with respect the center of the patch is given by $\rho(\lambda) = \sqrt{p_x^2 + p_y^2}$, and accounting for the parametric equation of the line $\rho(\lambda) = \sqrt{(O_{x} + \lambda t_{x})^2 + (O_{y} + \lambda t_{y})^2}$, subjected to $0 \leq \rho(\lambda) \leq R_S$. Solving the double inequality,
Artificial Ray–Tracing in Optical Systems (ARiOS)

Figure D.6: Solid Angle Determination (Cone of Sight) in Line to 3D Patch Intersection. (left) If the line is contained within the solid angles (i.e. cone of sight) determined by the 3D surface, there will exist an intersection point (P). Otherwise, the line will never intersect the surface (Q); (upper right) Inclination Angles ($\theta$) of the surface with respect to the origin of the line ($O_r$); (bottom right) Azimuthal Angles ($\phi$) of the surface with respect to the origin of the line ($O_r$).

**Figure D.7:** Determination of $\lambda$’s constraint limits in Line to 3D Patch Intersection. If, and only if, the line aims at the 3D patch, the point will intersect it. To determine the limits of the parametric constant $\lambda$ of the line, it is necessary to check whether the intersection point is contained in the surface ($0 \leq \rho(\lambda) \leq R_S$), or not.

\[
C_1 = (t_x^r)^2 + (t_y^r)^2 \\
C_2 = 2(O_x^t t_x^r + O_y^t t_y^r) \\
C_3 = (O_x^t)^2 + (O_y^t)^2 \\
C_4 = C_3 - R_S^2 \\
C_1 \lambda^2 + C_2 \lambda + C_3 = 0, \text{ if } 0 \leq \rho(\lambda) \\
C_1 \lambda^2 + C_2 \lambda + C_4 = 0, \text{ if } \rho(\lambda) \leq R_S
\]  

(D.39)

when $\lambda_1 = \lambda_2 = \lambda_3 = \lambda_4 \in \mathbb{C}$, the line has its origin in the center of the patch, and it is parallel to the z-axis. As a consequence, the line always will intersect the patch and the solution is unbounded. The remaining solutions give the lower and upper limit in $\lambda$ to carry out a proper optimization.

**Addendum: Handling a Successful Optimization**

Optimization methods control the increment of the variables to find a solution. Often, this increment is very sensitive to their order of magnitude. If the order of magnitude between variables is rather different, the algorithm will perform a permutation that affects them unequally. Hence, the algorithm will stop before finding a proper solution. To avoid this problem, a normalization of the involved variables is
in general a good practice. In this vein, the same increment will affect proportionally to all variables, independently of their orders of magnitude.

Then, using this approach requires of coding the variables to be in the same range before triggering the optimizer. Once the normalized variables go into the optimizer, an inverse normalization is required to solve the problem in the consistent system of units.

To code an original variable ranging in an interval $\psi \in (LB_\psi, UB_\psi)$, where $LB_\psi$ is the lower bound and $UB_\psi$ is the upper bound of the interval, into a normalized variable ranging in an interval $\hat{\psi} \in (\hat{LB}_\hat{\psi}, \hat{UB}_\hat{\psi})$, where $\hat{LB}_\hat{\psi}$ is the lower bound and $\hat{UB}_\hat{\psi}$ is the upper bound of the normalized interval, a linear transformation ($f(\psi)$) is used,

$$f(\psi) = \frac{\hat{UB}_\hat{\psi} - \hat{LB}_\hat{\psi}}{UB_\psi - LB_\psi} [\psi + \frac{UB_\psi - LB_\psi}{UB_\psi - LB_\psi} \frac{LB_\psi - LB_\psi}{UB_\psi - LB_\psi}]$$ (D.40)

whereas to decode the normalized variable ($\hat{\psi}$) into the original variable ($\psi$) a linear inverse transformation ($f^{-1}(\hat{\psi})$) is used,

$$f^{-1}(\hat{\psi}) = \frac{UB_\psi - LB_\psi}{UB_\psi - LB_\psi} [\hat{\psi} + \frac{UB_\psi - LB_\psi}{UB_\psi - LB_\psi} \frac{LB_\psi - LB_\psi}{UB_\psi - LB_\psi}]$$ (D.41)

### D.5 Aberrations in an Optical System

If an optical system is "perfect" a planar incident wave would result in a spherical wave after crossing the optical system, converging in a single point in the image plane. Similarly, a spherical incident wave would result in a planar wave after crossing the optical system. This behaviour follows the Fermat's principle that states that the path taken between two points by a ray of light, is the path that can be traveled in the least time.\(^\text{18}\) As a consequence, when the system is perfect the light has traveled the same distance for all points belonging to the same wavefront, and therefore it is in phase (before and after the optical system).

However, in a real optical system, due to different sources (e.g. geometry imperfections), the out-coming wavefront is not perfectly spherical (or planar) due to slight differences in the path traveled by light, and, thus, is not in phase. This phenomenon results in distorted (aberrated) images.\(^\text{19}\)

\(^{18}\) Malacara and Malacara 2003

\(^{19}\) Gross 2005
Ray Aberrations

All the deviations of a ray with respect to where it should have ideally impacted are called ‘Ray Aberrations’. Different ray aberrations can be distinguished (see in Figure D.8),

- The **Longitudinal Aberration** is the distance from the intersection point with a reference ray (i.e. the principal or chief ray) to a reference plane (i.e. the Gaussian image plane), measured along the reference ray or as a projection onto the optical axis (\(\Delta l'\)).

- The **Transverse Aberrations** are the lateral displacement components of the ray intersection point with a reference plane measured with respect to the intersection of the ideal reference point (\(\Delta y'\)).

- The **Angular Aberration** is equal to the relative deviation of its direction of propagation from that of an ideal reference ray (\(\Delta \theta'\)).

Transverse aberrations are very useful for understanding the spherical aberration, coma, or astigmatism, whereas Longitudinal aberrations are more useful to understand astigmatism or field curvature.

Spot Diagrams

A Spot Diagram is the set of intersection points with the image plane when all rays are traced from a fixed point on the object. Although it is a representation of the lateral ray deviations (see example in Figure D.9), it is difficult to distinguish and categorize typical aberrations.

The spot diagram represents a coma pattern mainly associated with keratoconus disease.
Wavefront Aberration

The wave aberration is defined as the optical deviation of the wavefront from a "Sphere of Reference" measured along a ray (see in Figure D.10). Generally, the converging rays should be concentric to a sphere centered on the image point and, according to the Fermat principle, the optical path length (i.e. the geometrical path traveled by the light through the system) to the image point should be constant. Deviations of the optical path length are errors which are measured as wave aberrations. The difference in optical path length of the rays \(OPL_i\) with respect to the optical path length of a main ray (i.e. chief ray, \(OPL_{CR}\)) is known as Optical Path Difference \((OPD)\), which is mainly related to the wavefront \((W)\) for all the points in the pupil \((x_p, y_p)\).

\[
W(x_p, y_p) = -OPD(x_p, y_p) = OPL_{CR} - OPL_i(x_p, y_p) \quad (D.42)
\]

Thus, the wavefront is dependent on the Chief Ray \((CR)\), and this will change with the object point under analysis. Generally speaking, the \(CR\) of an on-axis point (i.e. point located in the optical axis) is likely to have an image point close to the center of the image plane. On the contrary, the \(CR\) of an off-axis point is likely to have its intersection up to certain distance from the center. This detail is of great importance in the definition of the 'Sphere of Reference' \((SoR)\), and, as a consequence, in the definition of the wavefront. The \(SoR\) will be that one with

Figure D.10: Definition of the Wavefront Aberration. The wavefront aberrarion (in red) is the deviation with respect a perfect spherical wavefront (green line). The geometrical path traveled by light between surfaces times the refractive index of each medium, gives the optical path length. The difference of the optical path length for all rays with respect the optical path length of the Chief ray, gives the Optical Path Difference and, subsequently, the Wavefront \((W = -OPD = \sum n_j(dist(CR)_j - dist(R)_j))\).
the center in the intersection of the CR with the image plane, and the radius of curvature to the center of the Exit Pupil (ExP). Once the SoR is obtained, the intersection of all the rays passing through the optical system with the sphere are performed. Finally, the optical path length is calculated as the distance traveled from the object point to the intersection with the SoR.

Eventually, transverse aberrations are directly related to the wavefront as the slopes. Hence, the derivatives of the wavefront in x and y direction, provide the transverse aberrations of the system,

\[
\delta x' = F \frac{\partial W(x, y)}{\partial x} \\
\delta y' = F \frac{\partial W(x, y)}{\partial y}
\]

where \(F\) is a factor depending on the radius of the Sphere of Reference, and the refraction index of the image space (\(F = \frac{R_{SoR}}{n'}\)). Furthermore, knowing the wavefront \(W\) dependence on the Cartesian coordinates \((x, y)\), and the polar co-ordinates \((r, \theta)\), and applying the chain rule (see in Figure D.11),

\[
\frac{\partial W(r, \theta)}{\partial x} = \frac{\partial W(r, \theta)}{\partial r} \frac{\partial r}{\partial x} + \frac{\partial W(r, \theta)}{\partial \theta} \frac{\partial \theta}{\partial x} \\
\frac{\partial W(r, \theta)}{\partial y} = \frac{\partial W(r, \theta)}{\partial r} \frac{\partial r}{\partial y} + \frac{\partial W(r, \theta)}{\partial \theta} \frac{\partial \theta}{\partial y}
\]

the relation between transverse aberrations (in Cartesian coordinates) and the polar derivatives of \(W\) can be derived as,

\[
\delta x' = F\left(\frac{\partial W(r, \theta)}{\partial r} \cos \theta + \frac{\partial W(r, \theta)}{\partial \theta} \sin \theta\right) \\
\delta y' = F\left(\frac{\partial W(r, \theta)}{\partial r} \frac{-\sin \theta}{r} + \frac{\partial W(r, \theta)}{\partial \theta} \frac{\cos \theta}{r}\right)
\]

Finally, assuming that the wavefront is represented by an expansion of Zernike polynomials \((W(r, \theta) = \sum c_i Z_i(\rho, \theta))\), the relation between the transverse aberrations...
and the Zernike coefficients can be obtained,

\[
\begin{align*}
\frac{\delta x'}{F} &= \sum c_i \sum \left( \frac{\cos \theta}{R_{\text{pupil}}} \frac{\partial Z_i}{\partial \rho} - \frac{\partial Z_i}{\partial \theta} \frac{\sin \theta}{r} \right) \\
\frac{\delta y'}{F} &= \sum c_i \sum \left( \frac{\sin \theta}{R_{\text{pupil}}} \frac{\partial Z_i}{\partial \rho} + \frac{\partial Z_i}{\partial \theta} \frac{\cos \theta}{r} \right)
\end{align*}
\]  

(D.46)

With this relation, the wavefront can be reconstructed using the Zernike Polynomials and the transverse aberrations, which is essential in experimental aberrometers (e.g. Hartmann-Shack).^{21}

Image Quality and Astigmatism

Larry N. Thibos et al. give a reasonable compendium of quality metrics regarding wavefront aberrations (Accuracy and precision of objective refraction from wavefront aberrations^{22}). For example, the Peak-to-Valley difference is directly related with the flatness of the wavefront as,

\[
PV = \max(W(x,y)) - \min(W(x,y))
\]  

(D.47)

which is the difference between the highest and lowest points in the aberration map.

Many others can be used: metrics related to the wavefront slope (curvatures of the aberration maps, astigmatism map, blur-strength map), pupil fraction metrics (of less interest in our problem), or metrics of image quality for point objects (point-spread function, PSF, and derived relations) that will be implemented in the future to simulate human vision.^{23}

Furthermore, in ophthalmology, the sphero-cylindrical power (measured in diptres, D) and, then, the astigmatism of a patient, can be calculated based on the second-order Zernike coefficients (\(c_{pq}\)):

\[
\begin{align*}
M &= -\frac{c_0^4 \sqrt{3}}{R_p^2} \\
J_0 &= -\frac{c_2^2 \sqrt{6}}{R_p^2} \\
J_{45} &= -\frac{c_{2,-2}^2 \sqrt{6}}{R_p^2} \\
C_{yl} &= -2 \cdot \sqrt{J_0^2 + J_{45}^2} \\
\phi &= \frac{1}{2} \arctan \left( \frac{J_{45}}{J_0} \right) \\
Sph &= M - \frac{C_{yl}}{2}
\end{align*}
\]  

(D.48)
where $c_{m n}^m$ is the n-th order Zernike coefficient of meridional frequency $m$ (measured in microns), $R_p$ is the radius of the pupil (usually the iris), $J_\alpha$ is the ordinary cylinder of positive power $J$ at axis $\alpha$ and $M$ the spherical equivalent power of the lens, $Cyl$ is the cylindrical power, $\phi$ the angle of astigmatism, and $Sph$ the spherical power.\textsuperscript{24}

\section*{D.6 ARiOS Software}

\textbf{Design of the Software}

The design of the software is modular in such a way that different options can be activated or deactivated (see in Figure D.12). In this way, different features can be calculated efficiently. Currently, the main modules implemented are,

\begin{itemize}
  \item \textbf{Parsing Module}: allows for reading different file interfaces such as commercial data from topographers (Sirius, MODI, and Pentacam), user data in the form of numeric file (Label, x-coordinate, y-coordinate, z-coordinate), and user data in the form of Zernike coefficients (up to 91 coefficients are allowed). Besides, theoretical surfaces can be used (sphere, biconic, toric, and quadric surfaces).
  \item \textbf{Reconstruction Module}: allows for reconstructing the corneal surfaces using Zernike polynomials. The same pattern is evaluated so as to allow a proper pointwise comparison with other surfaces. Additionally, the Navarro’s schematic eye model is used to add the lens and the retina (fully customizables by user).
  \item \textbf{Curvature Module}: allows for computing the first and second derivatives of the Zernike surface in polar coordinates. Using the First and Second fundamental forms of the surface (see in Sec. D.3), the main curvatures, and subsequently the dioptres, of the surface are obtained.
  \item \textbf{Ray-Tracing Module}: allows for tracing rays in the optical system (see in Figure D.13). Besides, it also includes optimization procedures to obtain the Chief Ray,
\end{itemize}

and the Entrance and Exit Pupils. Currently, all the intersections are obtained using an optimization procedure and, thus, the process slows down considerably. However, since Zernike polynomials is an infinite series, the analytic solution is not trivial and will depend on the number of coefficients accounted for. On the contrary, the intersections with the Sphere of Reference and the retina are computed analytically, speeding up the computation considerably.

**Figure D.13: Ray-Tracing workflow in ARiOS software.** It allows to obtain the Chief Ray and Marginal Rays by means of an optimization procedure, the center and diameter of the Entrance and Exit Pupil of the system, and the ray-tracing of a light pattern. Subsequently, information coming out of the ray-tracing module can be processed to determine the aberrometry of the system, or the spot diagrams to assess in the vision’s quality of the patient.

- **Spot Diagram Module**: allows for computing the intersection points in different image planes once the Ray-Tracing Module has finished.
- **Wavefront Module**: allows for computing the Optical Path Difference for all the rays, and for deriving the Wavefront.
- **Report Module**: allows for creating \( \LaTeX \) reports automatically.

**ARiOS Input File (XML)**

For the definition of a problem (henceforth job), it is necessary to create an input file containing all the characteristics to compute a ray-tracing problem properly. The selected file format is XML,\(^{25}\) since it is versatile and widely spread in the scientific community. Two main sections can be distinguished depending on its aim: definition of the geometry, and definition of the optical properties of the media. Then, the brief view of the job is,

```xml
<?xml version='1.0' encoding='ISO-8859-1'?>
<ariOS_spec version='0.0'>
  <OpticalSystem type='Default'>
    Definition of corneal geometry
    Definition of pupillary geometry
    Definition of Examination conditions
    Definition of lens geometry
    Definition of retinal geometry
  </OpticalSystem>
</ariOS_spec>
```

\(^{25}\) Cerami 2005
Definition of Geometry

Geometrical features can be defined inside the ‘Optical System’ section. The hierarchy of the module comprises,

**Cornea**

This section contains the definition of the corneal features. Two attributes can be defined: type and diameter. Type is used to define whether the surface is externally provided using a commercial or user-defined file, or it is provided using an analytic surface. Diameter defines the maximum diameter of the surface (i.e. remove points beyond the defined limit in the user files, or it defines the limit up to what the analytic surface is defined).

When the attribute keyword type is used to call an external file, three different features separated by ‘::’ are needed (e.g. ‘type = FreeForm::drogon::sirius’),

- FreeForm, which states that the file is going to be provided in a free form.

- foo.extension, which is the name of the external file. Usually, it is provided without extension (providing that the extension is accepted by the software: ‘.csv’, ‘.xlsx’, ‘.dat’, ‘.inp’, ‘.txt’).

- device, which defines the type of external file: ‘sirius’, ‘modi’, ‘pentacam’, ‘fem’, ‘zernike’. To load commercial files ‘sirius’, ‘modi’, ‘pentacam’ can be used, whereas to load user files ‘fem’ (surface represented by cartesian point cloud), or ‘zernike’ (surface defined by zernike coefficients) are used.

In detail, the external files that can be provided are the following,

- **Commercial files**, different topographers are currently supported (‘.csv’, ‘.xlsx’),
  - Sirius (CSO, Italy). This topographer provides the corneal thickness, and the elevation of the anterior and posterior surfaces. The file is provided in polar coordinates, defining 31 rings (from 0 to 6 mm in radius, and increments of 0.2 mm) with 256 points (from 0 to $2\pi$ radians).
- MODI (CSO, Italy). It is analogous to Sirius, but with less capabilities. Only the anterior surface is provided, keeping the same format definition.

- Pentacam (Oculus, Germany). This topographer provides 2 files: the first one containing the corneal thickness, and the second one containing the elevation (i.e. sagitta) of the anterior and posterior surfaces. The file format is a Cartesian matrix of dimension 141x141 containing the data of interest (thickness, elevation), and ranging from -7 to 7 mm with increments of 0.1 mm (both in x and y directions).

- **User-defined files**, two different kinds of input files are currently supported by the software: defining the Cartesian coordinates of the surface, or defining the Zernike coefficients of the surface. One file for each surface is needed (e.g. ‘drogon_anterior.inp’, ‘drogon_posterior.inp’). When calling an external file, it is not necessary to add the ‘_anterior’ or ‘_posterior’ labels, since the software automatically fills them. Only the root of the name (e.g. ‘drogon’) is required.

  - User-defined file of Cartesian coordinates (‘.dat’, ‘.inp’, ‘.txt’). Each row contains the label of the node (optionally), and the \((x, y, z)\) coordinates of each point.

  - User-defined file of Zernike coefficients, containing the maximum radius (i.e. the pupil radius) of the surface (first row), the location of center of the surface \((x - \text{second row}, y - \text{third row}, z - \text{fourth row})\), and up to 91 Zernike coefficients representing up to 12th order of the Zernike polynomials (fifth row in ahead).

When the attribute keyword type is used to generate an analytic surface, only one feature is needed: the type of analytic surface (e.g. type = sphere). Different tags can be used depending on the surface to generate: ‘sphere’, ‘biconic’, ‘ellipsoid’, ‘toric’. To complete the definition of an analytic surface, different features need to be defined:

- Location of the apex (VertexReference), which is the triplet of coordinates defining the apex of the eye.

- Radius of the anterior/posterior surface in x/y direction (AnteriorRadius_x, AnteriorRadius_y, PosteriorRadius_x, PosteriorRadius_y). If a sphere is defined, only the direction x is used.

- Asphericity of anterior/posterior surface in x/y direction (AnteriorAsphericity_x, AnteriorAsphericity_y, PosteriorAsphericity_x, PosteriorAsphericity_y).

- Rotation of the anterior/posterior surface (Anterior_Rotation, Posterior_Rotation). This feature allows to rotate the surface a certain angular degree.
The use of radians, or angular degrees is controlled by the attribute keyword units (e.g. `units = 'deg'`, or `units = 'rad'`).

- Central corneal thickness (CCT), which defines the separation between anterior and posterior surfaces in millimeters.

- Definition of anterior/posterior ellipsoidal surfaces by means of the semi-axes `AnteriorSemiaxis_a, AnteriorSemiaxis_b, AnteriorSemiaxis_c, PosteriorSemiaxis_a, PosteriorSemiaxis_b, PosteriorSemiaxis_c`.

**Pupil**

Currently, only circular pupils, centered or decentered, can be defined by the `(x, y)` coordinates of the center position (Center), and the radius (Radius). The z-coordinate of the pupil is provided by the height of the anterior chamber, defined in the next section (Examination Conditions).

**ExaminationConditions**

The examination conditions allow to define the distance of the pupil (i.e. iris) with respect to the apex using the height of the anterior chamber (ChamberHeight). Regarding the accommodation of the eye, currently only far objects (infinity) are implemented. In further updates, more features will be added.

**Lens**

Currently, the definition of the crystalline is done using the Navarro’s schematic eye model (see in Figure D.5). Their surfaces are defined as biconic analytical surfaces. The modification of the parameters is not encouraged. However, the radius, asphericity, and position of the vertices of both surfaces can be directly controlled by user.

**Retina**

Currently, the definition of the retina is done using the Navarro’s schematic eye model (see in Figure D.5). The surface is defined as a spherical analytical surface. The modification of parameters is not encouraged. However, the radius, asphericity, and center of the retina can be directly controlled by user.
Complete extract of all available geometrical features accessible to user modification,

```
<OpticalSystem type='Default'>
  <Cornea type='FreeForm::foo.extension::device' diameter='9'>
    <VertexReference>0.0,0.0,0.0</VertexReference>
    <AnteriorRadius_x>7.72</AnteriorRadius_x>
    <AnteriorAsphericity_x>-0.26</AnteriorAsphericity_x>
    <AnteriorRadius_y>7.72</AnteriorRadius_y>
    <AnteriorAsphericity_y>-0.26</AnteriorAsphericity_y>
    <Anterior_Rotation units='deg'>0</Anterior_Rotation>
    <CCT>0.55</CCT>
    <PosteriorRadius_x>6.5</PosteriorRadius_x>
    <PosteriorAsphericity_x>0.0</PosteriorAsphericity_x>
    <PosteriorRadius_y>6.5</PosteriorRadius_y>
    <PosteriorAsphericity_y>0.0</PosteriorAsphericity_y>
    <Posterior_Rotation units='deg'>0</Posterior_Rotation>
    <AnteriorSemiaxis_a>7.2</AnteriorSemiaxis_a>
    <AnteriorSemiaxis_b>7.2</AnteriorSemiaxis_b>
    <AnteriorSemiaxis_c>7.2</AnteriorSemiaxis_c>
    <PosteriorSemiaxis_a>6.5</PosteriorSemiaxis_a>
    <PosteriorSemiaxis_b>6.5</PosteriorSemiaxis_b>
    <PosteriorSemiaxis_c>6.5</PosteriorSemiaxis_c>
  </Cornea>
  <Pupil type='Default'>
    <Center>0.0, 0.0</Center>
    <Radius>3</Radius>
  </Pupil>
  <ExaminationConditions type='Default'>
    <ChamberHeight>3.6</ChamberHeight>
    <Accommodation>Infinity</Accommodation>
    <EyePosition>Right</EyePosition>
  </ExaminationConditions>
  <Lens type='Default' diameter='10'>
    <AnteriorRadius>10.2</AnteriorRadius>
    <AnteriorAsphericity>-3.1316</AnteriorAsphericity>
    <AnteriorVertex>3.6</AnteriorVertex>
    <PosteriorRadius>6.0</PosteriorRadius>
    <PosteriorAsphericity>-1.0</PosteriorAsphericity>
    <PosteriorVertex>7.6</PosteriorVertex>
  </Lens>
  <Retina type='Default' diameter='22'>
    <Center>12.0</Center>
    <Radius>-12.0</Radius>
    <Asphericity>0.0</Asphericity>
  </Retina>
</OpticalSystem>
```
Definition of Optical Media

Once the geometry of the optical system is defined, it is necessary to build the physical conditions (light and refractive indices) to solve the ray-tracing problem. Inside the job, the Media section contains all the necessary information split into three main subsections.

Light

This section allows to define,

- the type (Type) of light source (currently only punctual light sources are available),
- the position (Position) with respect the optical axis (on-axis, off-axis),
- the distance from the light source to the apex along the optical axis in negative millimeters (Distance2Apex),
- the location of the light source in the object plane (InPlaneLocation), which can be angular (typically) or cartesian, and that are defined by the angle (or position) with respect the retina in x and y meridian (e.g. 15, 0 represents 15° in the nasal-temporal plane and 0° in the superior-inferior plane),
- the radius of the pencil of light going into the system (Rpencil),
- the direction of the axis under analysis (VisionAxis, currently only the optical axis),
- and the plane of evaluation (or user Exit Pupil), where the wavefront is evaluated. Currently it is of extreme importance to locate it after the crystalline, where all the optical path lengths can be properly calculated. Two attributes can be controlled: type, and z_coord. With type the user can control whether the evaluation plane is located at the physical pupil (ExitPupil) or in a user-defined plane (user). The location of the user-defined plane can be controlled by z_coord.

RefractiveIndex

This section controls the definition of the refractive indices. It has two attribute keywords: chromatic and wavelength. Chromatic controls whether the refractive indices should include chromatic dispersion (using the Herzberger formulas) or not. If no chromatic effect is desired, the user can introduce manually the refractive index of each medium using the tag chromatic = 'user', and defining
the different media (air, cornea, aqueous humor, lens, vitreous humor). On the contrary, if chromatic dispersion is to be included, the user can define the tag chromatic = 'single' along with the wavelength of the light in nanometers (e.g. wavelength='587'). In this vein, the Herzberger formulas will be applied to compute the refractive indices.  

Pattern

This section controls the light pattern that will be analyzed (type = 'rectangular', type = 'polar'), the number of total points (TotalPoints) that want to be analyzed along the radius (or semi-axis), the number of total points along the circular rings (PointsPerRing, only applicable if a polar type is used), and the seed (Seed) of the points along the radius (or semi-axis). The seed is used to set a uniform distribution of points (type = 'uniform'), or a more dense distribution of points in the periphery (type = 'single_ratio'). The minimum size of the increment can be controlled using the variable MinSeed, and a finer increment towards the border of the radius (or x semi-axis) can be controlled with Bias_1. Also a finer increment towards the border of the y semi-axis (only in rectangular mode) can be applied (type = 'double_ratio') by controlling a second variable (Bias_2). Finally, an exclusion factor (ExclusionFactor) is used to control up to what percentage of the center of the pattern will keep the minimum size of the increment before starting to refine (see different examples in Figure D.14).

Figure D.14: Different Light Patterns available in ARiOS. (a) Uniform cartesian pattern with a total of 8 points in semi-axial direction; (b) Uniform polar pattern with a total of 8 points in radial direction; (c) Single biased Cartesian pattern in x-direction. Central area keeps a constant seed, and towards the periphery it becomes finer; (d) Single biased polar pattern.
Complete extract of all available optical media features accessible to user modification,

```xml
<Media schema='Default'>
  <Light type='geometric'>
    <Type>Punctual</Type>
    <Position>on-axis</Position>
    <Distance2Apex>-6000.0</Distance2Apex>
    <InPlaneLocation type='angular'>15,0</InPlaneLocation>
    <Rpencil>3.0</Rpencil>
    <VisionAxis>0.0,0.0,1.0</VisionAxis>
    <Evaluation_Plane type='exit_pupil' z_coord='8.6'/>
  </Light>
  <RefractiveIndex chromatic='default' wavelength='587'>
    <Air>1.0</Air>
    <Cornea>1.3375</Cornea>
    <AqueousHumor>1.3374</AqueousHumor>
    <Lens>1.420</Lens>
    <VitreousHumor>1.336</VitreousHumor>
  </RefractiveIndex>
  <Pattern type='rectangular'>
    <TotalPoints>8</TotalPoints>
    <PointsPerRing>6</PointsPerRing>
    <Seed type='single_ratio'>
      <MinSeed>0.1</MinSeed>
      <Bias_1>0.2</Bias_1>
      <Bias_2>0.2</Bias_2>
      <ExclusionFactor>0.4</ExclusionFactor>
    </Seed>
  </Pattern>
</Media>
```

Example of Usual Jobs

Corneal geometry provided by External Commercial File

Corneal geometry comes from a Sirius topographer with an analysis diameter of 10 mm. The light source is punctual, on-axis, located at 6 meters (infinite), and with a light pencil radius of 2.5 mm (which means that only 5 mm in diameter of the cornea is illuminated). The light’s wavelength is 587 nm, and chromatic dispersion is included. The corneal illumination pattern follows an uniform polar pattern with 10 points in the radius (10 rings), and 10 points per ring. Finally, the wavefront aberration is evaluated in a plane located 10 mm inside the eye, right after the complete optical system.
Methods for Characterising Patient–Specific Corneal Biomechanics

Corneal geometry provided by External User File (Cartesian Point Cloud)

Corneal geometry is provided by 2 external files (`drogon_anterior.inp`, `drogon_posterior.inp`). The file contains the Cartesian coordinates of the surfaces.

**Example of Corneal File (drogon_anterior.inp):**

```
# Label, x, y, z
1 0.0 0.0 0.0
2 0.2 0.0 0.1
...
66666 3.0 3.0 2.57
```

**Example of ARiOS’ job (drogon.arios)**

```xml
<?xml version='1.0' encoding='ISO-8859-1'?>
<ariOS_spec version='0.0'>
  <OpticalSystem type='Default'>
    <Cornea type='FreeForm::drogon::sirius' diameter='10'>
    </Cornea>
  </OpticalSystem>
  <Media schema='Default'>
    <Light type='geometric'>
      <Type>Punctual</Type>
      <Position>on-axis</Position>
      <Distance2Apex>-6000.0</Distance2Apex>
      <Evaluation_Plane type='user' z_coord='10'/>
      <Rpencil>2.5</Rpencil>
    </Light>
    <RefractiveIndex chromatic='single' wavelength='587'/>
  </Media>
</ariOS_spec>
```
<Light type='geometric'>
  <Type>Punctual</Type>
  <Position>on-axis</Position>
  <Distance2Apex>-6000.0</Distance2Apex>
  <Evaluation_Plane type='user' z_coord='10'/>
  <Rpencil>2.5</Rpencil>
</Light>

<RefractiveIndex chromatic='single' wavelength='587'>
</RefractiveIndex>

<Pattern type='polar'>
  <TotalPoints>10</TotalPoints>
  <PointsPerRing>10</PointsPerRing>
  <Seed type='uniform'>
  </Seed>
</Pattern>

Cornea provided by External User File (Zernike Coefficients)

Corneal geometry is provided by 2 external files ('drogon_coefficients_anterior.inp', 'drogon_coefficients_posterior.inp'). The files contain the radius of the pupil needed to adjust the Zernike polynomials, the triplet of coordinates defining the center of the surface, and up to 91 Zernike coefficients defining the surface. The light source is off-axis, located at 30° with respect to the retinal center in the superior-inferior plane. Refractive indices are provided by user. Pattern of light is uniform and rectangular.

Example of Corneal File (drogon_coefficients_anterior.inp)

#Identifier, value
-1 3  # Radius
-1 0.0  # X-coord
-1 0.0  # Y-coord
-1 0.55  # Z-coord
1 0.156  # 1st Zernike Coefficient
2 0.0  # 2nd Zernike Coefficient
3 0.0  # 3rd Zernike Coefficient
4 -0.045  # 4th Zernike Coefficient
...
91 0.0  # 91st Zernike Coefficient

Example of ARiOS' job (drogonarios)

<?xml version='1.0' encoding='ISO-8859-1'?>
<ariOS_spec version='0.0'>
  <OpticalSystem type='Default'>
Methods for Characterising Patient–Specific Corneal Biomechanics

Analytic Cornea: Torus

The anterior surface of the cornea is defined by a torus with $R_x = 7$ mm, $R_y = 8$ mm. The posterior surface of the cornea is defined by a torus with the same radii but rotated $30^\circ$. 
D.7 Validation

Different optical configurations were computed in both ARiOS (in-house optical software), and OSLO (Lambda Research Corporation). To validate the results, the same geometry, properties, and evaluation planes were used. Besides, the main Zernike coefficients related to astigmatism ($Z_3$, $Z_4$, $Z_5$, $Z_{12}$, microns) and to coma ($Z_7$, $Z_8$, in microns), the wavefront (qualitative distribution, and Peak-to-Valley values), and the spot diagrams (qualitative pattern, and dispersion) were used as control features to check whether ARiOS was accurate enough, or not, with respect a well consolidated optical software.

A three-step validation was performed:

- **Theoretical simple surfaces**, three different cases composed of a single analytic surface (separating 2 optical media, air–cornea) were analyzed.

- **Complex analytical surfaces**, one case simulation of the structures of the human eye. The corneal surfaces are defined by two different analytic surfaces.

- **Real simple surfaces**, two different real cases (normal and keratoconus eyes) composed of 2 real topographic surfaces (separating 3 optical media, air–cornea–anterior chamber) were analyzed.

**Theoretical Single Surfaces**

Three different simple analytic surfaces were analyzed:
Table D.7: Validation ARiOS: Simple Surfaces. Comparison between OSLO results and ARiOS results for the same cases (1, 2, and 3), and the same control variables. All units in mm.

<table>
<thead>
<tr>
<th>Case</th>
<th>1 (OSLO)</th>
<th>1 (ARiOS)</th>
<th>2 (OSLO)</th>
<th>2 (ARiOS)</th>
<th>3 (OSLO)</th>
<th>3 (ARiOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piston ($Z_0$)</td>
<td>-34.58</td>
<td>-34.5876</td>
<td>-26.44</td>
<td>-26.8358</td>
<td>-25.624</td>
<td>-26.5459</td>
</tr>
<tr>
<td>Vert. Astigm. ($Z_5$)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary Spherical ($Z_{12}$)</td>
<td>0.269941</td>
<td>0.2699</td>
<td>-</td>
<td>0.4204</td>
<td>-</td>
<td>0.4101</td>
</tr>
</tbody>
</table>

*Table Legend and Units.* Zernike Coefficients ($Z_0$, $Z_3$, $Z_4$, $Z_5$, $Z_{12}$, microns); $rW_{x,y}$ radii of the wavefront in x and y direction (mm); Peak-to-Valley values of the Wavefront ($P - V_x$, $P - V_y$, $P - V_t$, microns).

- **Case 1:** Sphere of radius 8 mm, pupil diameter of 6 mm, and described by the following Zernike coefficients (in microns): $Z_0 = 288.2161$, $Z_4 = 168.4806$, $Z_{12} = 1.6468$, $Z_{24} = 0.0316$.

- **Case 2:** Torus of 2 different radii ($R_x = 7$, and $R_y = 8$ mm), pupil diameter of 6 mm, and described by the following Zernike coefficients (in microns): $Z_0 = 309.9117$, $Z_4 = 181.4990$, $Z_5 = 18.0745$, $Z_{12} = 2.0438$, $Z_{13} = 0.4655$, $Z_{14} = 0.1975$, $Z_{24} = 0.0453$, $Z_{25} = 0.0153$, $Z_{26} = 0.0068$, $Z_{27} = 0.0043$.

- **Case 3:** Torus of 2 different radii ($R_x = 7$, and $R_y = 8$ mm), 30° clockwise-rotation, pupil diameter of 6 mm, and described by the following Zernike coefficients (in microns): $Z_0 = 309.9117$, $Z_3 = -15.653$, $Z_4 = 181.4990$, $Z_5 = 9.0372$, $Z_{10} = -0.1711$, $Z_{11} = -0.4031$, $Z_{12} = 2.0438$, $Z_{13} = 0.2327$, $Z_{14} = -0.0988$, $Z_{22} = -0.0059$, $Z_{23} = -0.0132$, $Z_{24} = 0.0453$, $Z_{25} = 0.0076$, $Z_{26} = -0.0034$, $Z_{27} = -0.0043$.

Results of the commercial software versus results of the in-house optical software are in good agreement (see in Table D.7).

Although rather small differences exist, they can be mainly associated with the number of rays used for the ray-tracing. The more dense the ray-tracing, the more precise the wavefront reconstruction.27

**Theoretical Complex System**

The distances and refractive indices used in the optical system are defined in Figure D.15. The anterior and posterior surfaces of the cornea correspond to the toruses of Case 2 and 3, respectively.
Wavefront aberrations (see in Figure D.16, left panel), and spot diagrams are in good agreement. Once again and despite small differences, Zernike reconstructions of the Wavefronts are in good agreement (see in Table D.8). This small perturbations are related to the great difference in the amount of trace rays (OSLO vs. ARIOS).

Table D.8: Validation ARIOS: Zernike Reconstruction of the Wavefront (Theoretical Complex System). Amplitude of the coefficients is in microns.

<table>
<thead>
<tr>
<th></th>
<th>OSLO</th>
<th>ARIOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_0$</td>
<td>-13.298</td>
<td>-12.325</td>
</tr>
<tr>
<td>$Z_3$</td>
<td>1.294</td>
<td>1.294</td>
</tr>
<tr>
<td>$Z_4$</td>
<td>-3.033</td>
<td>-2.391</td>
</tr>
<tr>
<td>$Z_5$</td>
<td>14.837</td>
<td>15.076</td>
</tr>
<tr>
<td>$Z_7$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$Z_8$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$Z_{11}$</td>
<td>0.068</td>
<td>0.113</td>
</tr>
<tr>
<td>$Z_{12}$</td>
<td>3.986</td>
<td>4.278</td>
</tr>
<tr>
<td>$Z_{13}$</td>
<td>0.884</td>
<td>1.533</td>
</tr>
</tbody>
</table>
Real Surfaces

In this section, real surfaces are used to validate patient-specific reading and ray-tracing. Only the cornea is taken into account, disregarding the internal structures (see in Figure D.17). To analyze different corneal areas, two different radii of the light pencil are used: 1 and 3 mm.

Figure D.17: Dimensions of Real System for ARIOS Validation. Distances between surfaces and refractive indices are shown in figure. Anterior and posterior cornea are the real surfaces corresponding to a normal and keratoconus eye, respectively. Retina is defined using the schematic eye model of Navarro.

Normal Eye

Apart from the wavefront validation, since revolution surfaces are no longer used, normal eye is also used to check the registration of the surfaces in both software (ARIOS and OSLO). Only the anterior surface of the cornea is accounted for. Two different radii of light pencil (1 and 3 mm), and image plane distances (31.1504 and 31.7096 mm) are used. Qualitatively, the same distributions of the spot diagrams are obtained for all the combinations, showing a proper computation and positioning of the surfaces (see in Figure D.18).

Subsequently, both surfaces of the cornea are incorporated, and the same analysis is carried out: two different radii of light pencil (1 and 3 mm), and image plane distances (31.1504 and 31.7096 mm). Figure D.19 shows the spot diagrams for the complete cornea of the normal eye for the 4 analyzed combinations. Qualitatively, the same distributions of the spot diagrams are obtained for all the combinations, showing a proper computation and positioning of the surfaces.

Finally, following the description of the problem depicted in Figure D.17, the wavefront of the normal cornea is analyzed using two radii of light pencil: 1 and 3 mm. Figures D.20 and D.21 show a good agreement in both, spot diagram and wavefront reconstruction. Furthermore, this fact is also supported by Table D.9. Although,
slight differences are found, these are mainly related with the different amount of
rays used to perform the ray-tracing (OSLO vs. ARiOS).
Figure D.20: Validation ARIOS: Wavefront of Normal Eye (1 mm). (upper panel) OSLO results: (left) spot diagram, (right) wavefront reconstruction; (bottom panel) ARIOS results: (left) spot diagram, (right) wavefront reconstruction. All units in mm.

Figure D.21: Validation ARIOS: Wavefront of Normal Eye (3 mm). (upper panel) OSLO results: (left) spot diagram, (right) wavefront reconstruction; (bottom panel) ARIOS results: (left) spot diagram, (right) wavefront reconstruction. All units in mm.
Table D.9: Validation ARiOS: Zernike Coefficients of Wavefront (Normal Eye).

<table>
<thead>
<tr>
<th></th>
<th>O. (1 mm)</th>
<th>A. (1 mm)</th>
<th>O. (3 mm)</th>
<th>A. (3 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Z_0$</td>
<td>0.150</td>
<td>-0.142</td>
<td>-0.520</td>
<td>-0.505</td>
</tr>
<tr>
<td>$Z_3$</td>
<td>0.023</td>
<td>0.022</td>
<td>0.291</td>
<td>0.362</td>
</tr>
<tr>
<td>$Z_4$</td>
<td>-0.081</td>
<td>-0.079</td>
<td>-0.051</td>
<td>-0.053</td>
</tr>
<tr>
<td>$Z_5$</td>
<td>-0.021</td>
<td>-0.026</td>
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<td>0.011</td>
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<tr>
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<tr>
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<td>0.003</td>
<td>0.184</td>
<td>0.181</td>
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<tr>
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<td>-0.003</td>
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</table>

**KTC Eye**

Following the description of the problem depicted in Figure D.17, the wavefront of the KTC cornea is analyzed using two radii of light pencil: 1 and 3 mm. Figures D.22 and D.23 show a good agreement in both, spot diagram and wavefront reconstruction. Furthermore, this fact is also supported by Table D.10. Although, slight differences are found, these are mainly related with the different amount of rays used to perform the ray-tracing (OSLO vs. ARiOS).
Methods for Characterising Patient–Specific Corneal Biomechanics

Figure D.23: Validation ARiOS: Wavefront of KTC Eye (3 mm). (Upper panel) OSLO results: (left) spot diagram, (right) wavefront reconstruction; (bottom panel) ARiOS results: (left) spot diagram, (right) wavefront reconstruction. All units in mm.

Table D.10: Validation ARiOS: Zernike Coefficients of Wavefront (KTC Eye). (Columns 2-3) Zernike reconstruction of corneal wavefront for a light radius of 1 mm; (Columns 4-5) Zernike reconstruction of corneal wavefront for a light radius of 3 mm. (O.) OSLO results; (A.) ARiOS results.

<table>
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<tr>
<th></th>
<th>O. (1 mm)</th>
<th>A. (1 mm)</th>
<th>O. (3 mm)</th>
<th>A. (3 mm)</th>
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<td>-0.006</td>
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Conclusions

ARiOS has proved a great performance when compared against a well-established commercial software (OSLO). It is able to load commercial files, to determine the curvatures of the surface, and to perform the ray-tracing providing accurate spot-diagrams and wavefront reconstructions. The small errors found are related with the number of rays traced by each software. The higher the complexity of the surface, the greater the amount of traced rays required. While OSLO uses a great amount of rays, ARiOS still uses a relative small amount (500 rays in 7-8 minutes). Since for each intersection it carries out an optimization and is still in development, the performance in terms of execution time needs to be highly improved. However, its accuracy is enough to be used as research tool in opto-mechanical simulations.
Bibliography


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