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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 determine the intraocular pressure (IOP) and the quality of corneal tissue. In contrast to the physiological state of stress of the cornea, tonometers induce non-physiological bending stress. Recently, the use of a single experiment to calibrate a set 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, restricting the optimization space to circumvent the ambiguity of the fitting. For the first time, both corneal behaviors, i.e., biaxial tension (physiological) and bending (non-physiological), are taken into account. The experimental protocol was performed using an animal model (New Zealand rabbit's cornea). The patient-specific geometry and IOP were registered using a MODI topographer (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 the 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 surgeries, indicating that the protocol can provide a reliable set of mechanical properties that enables further applications and simulations. After a reliable ex vivo database of inflation experiments is built, our protocol could be extended to humans.

1. Introduction

In visual healthcare, an increasing number of efforts are being made toward proper corneal characterization to assess refractive surgeries (Studer et al., 2013), to study the effect of intracorneal segment rings (ICRS) in keratoconus stabilization (Kymionis, 2015), to plan better surgical interventions, and to qualitatively predict the evolution of a pathology (Romero-Jiménez et al., 2010; Summers and Harper, 2015). 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 (Piñero and Alcón, 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., biaxial tension due to the IOP; see white point in Fig. 1a), the embedded collagen fibers are under tension and contribute to load bearing. However, during a tonometry test, the stress
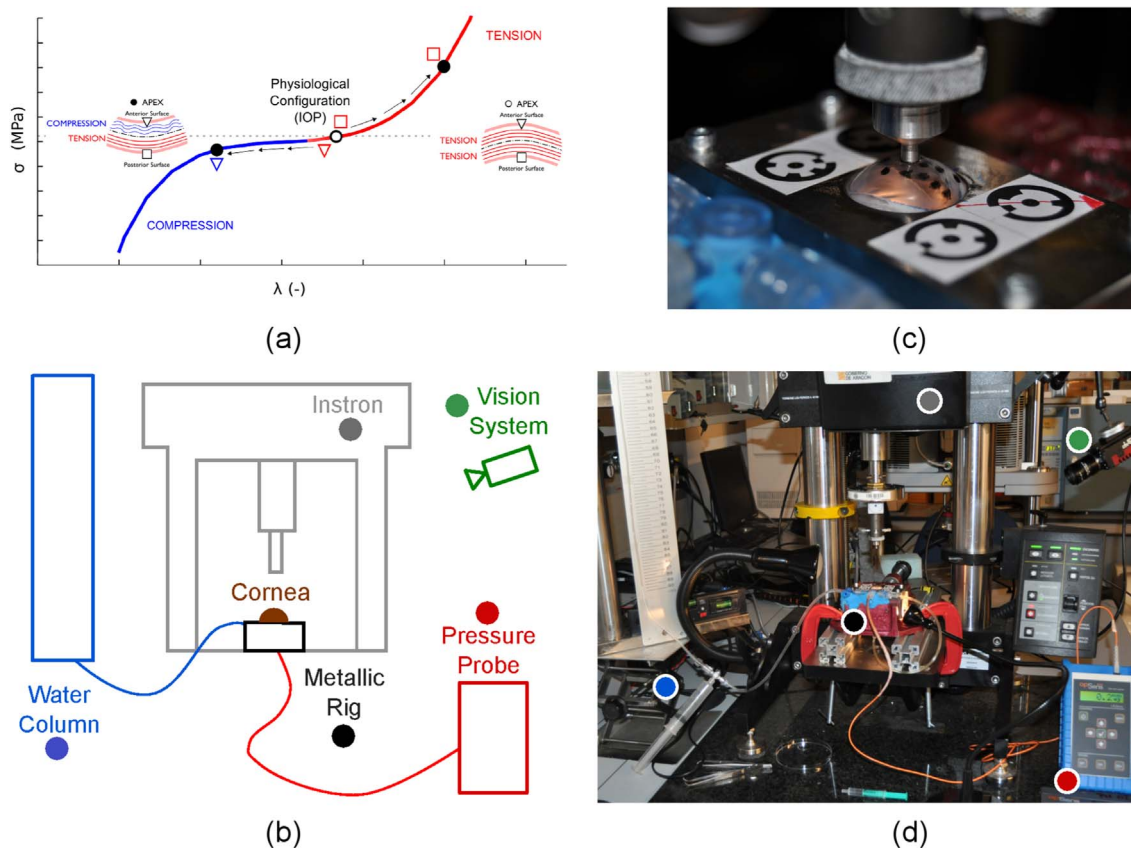
Fig. 1. Experimental protocol. (a) *Mechanical response of the corneal stroma.* Due to the physiological IOP, the anterior and posterior stroma are under normal tension (see the square and inverted triangle close to the white dot). When an indentation is applied, the cornea bends. Thus, the anterior 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)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

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 Fig. 1a).

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 (Pandolfi and Holzapfel, 2008; Elsheikh et al., 2013). These models represent the corneal behavior observed in experiments (Bryant and McDonnell, 1996; Elsheikh et al., 2015). Currently, different experimental protocols are used to characterize the corneal tissue: uniaxial tensile tests (Pandolfi and Boschetti, 2015), vibration tests (Kling et al., 2014), and inflation tests (Elsheikh et al., 2015). 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.

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) (Girard et al., 2009a, 2009b; Nguyen and Boyce, 2011) 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 (Hayes et al., 2007; Thomasy et al., 2014; Guo Yu et al., 2014), in our experiments, the surgery had the opposite effect of increasing astigmatism. To control the corneal optics, 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 (Carvalho, 2005). Finally, before the refractive surgery, the optical outcomes were predicted using the optimal set of material parameters on average and patient-specific geometries.

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 (see Section 2.1) collects all the information regarding the experimental characterization: the selection of animals and ethics guidelines (see Section 2.1.1), the geometrical characterization and the measurements of intraocular pressure (see Section 2.1.2), the mechanical characterization of the cornea via inflation and experimentation experiments (see Section 2.1.3), and the in vivo ocular refractive surgery performed to validate the model (see Section 2.1.4). Second,