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Biomechanics of the human lens and accommodative system: Functional relevance to physiological states

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ABSTRACT

The ability of the human lens to accommodate is mediated by the ciliary muscle and zonule; the manifest optical power changes depend on the shape and material properties of the lens. The latter are difficult to measure with accuracy and, given the dynamic aspects of accommodation and the ageing of cells and tissues, the biomechanics of the lens is neither fixed nor constant. A range of techniques have been developed to measure both ageing trends and spatial variations in the mechanical properties and these have yielded a diverse array of findings and respective conclusions. The majority of quasi-static measurements, where the observation time is in minutes or hours, indicate that the stiffness of the lens increases with age at a faster rate in the lens centre than in the periphery. Dynamic measurements show that lens material properties are dependent on the loading frequency. Recent *in vivo* analyses suggest that, along the optic axis, profiles of elastic moduli are very similar to profiles of refractive index. This review assesses the advantages and limitations of different measurement techniques and consequent variations in elastic moduli that have been found. Consideration is given to the role of computational modelling and the various modelling methods that have been applied. The changes in mechanical properties of the lens associated with ageing and pathology and future implications for implant design are discussed.

1. Introduction

The human eye is a well-designed optical and biological system designed to meet the visual demands of the subject. The focussing power of human eye is supplied by the combined refractive powers of the cornea and lens with the latter providing the capacity to alter and adjust focus by the process of accommodation.

The lens is a lamellar structure composed of long fibre cells in each layer containing proteins (crystallins) and water and enclosed within a transparent basement membrane or capsule (Fig. 1). The capsular thickness is approximately 10 μm with localised variations (Barraquer et al., 2006). Lens growth is initiated from the epithelial cells that line the anterior capsule and which migrate from the pole to the equator (Fig. 1) where differentiation to lens fibres takes place (reviewed in Bassnett and Šikić, 2017). Although there is no clear demarcation, the lens is considered to have two major sections: a central nucleus, with a radial diameter that occupies approximately two-thirds of the lens and a surrounding cortex (Brown, 1973; Sparrow et al., 1986). Within the latter, different zones, linked to stages of growth and development have been identified optically (Koretz et al., 1994, 2002), morphologically (Donaldson et al., 2017) and clinically (Sparrow et al., 1986). These have been labelled as C1, C2, C3 and C4 successively from the outermost to the innermost layer (Sparrow et al., 1986) as shown in Fig. 1.

1.1. Current theories of accommodation

The accommodative theory, postulated by Helmholtz (1855), has stood the test of time and remains the most widely supported and cited despite alternative theories proposed subsequently (Coleman, 1970; Fincham, 1937; Schachar, 1992; Tscherning, 1904). According to Helmholtz the ciliary muscle relaxes in order to focus on distant objects, increasing tension in all parts of the zonule. This in turn imparts force, via the capsule, on the lens, stretching and reducing its curvature. For near focussing, the ciliary muscle contracts, releasing zonular tension and causing the lens to assume a more curved shape (Fig. 2a).

The relaxation of the ciliary muscle for increased accommodative effort, may appear to be counter-intuitive and was challenged by those who proposed that ciliary muscle contraction increased zonular tension and curvature in the axial and paraxial regions of the lens (Fincham, 1937; Tscherning, 1904). The force of the vitreous on the posterior surface of the lens was postulated by Coleman (1970), Coleman and Fish (2001) to play a role in accommodation.

Schachar (1992, 1994) has considered the different contribution of zonular sections on accommodation, proposing that, with accommodation, the equatorial zonule increases in tension as the ciliary muscle contracts thereby causing a concomitant relaxation of the anterior and posterior zonule. This results in the lens assuming a spindle shape with steep central and flat peripheral surfaces (Schachar, 1992,

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Abbreviations

BLS	Brillouin Light Scattering
OCE	Optical Coherence Elastography
DMA	Dynamic Mechanical Analysis
AFM	Atomic Force Microscopy
FE	Finite Element
AIOL	Accommodative Intraocular Lens

Most investigations on the biomechanics of the lens have been conducted on *in vitro* lenses, ie, the lens spinning (Fisher, 1971; Burd et al., 2011; Wilde et al., 2012), indentation (Heys et al., 2004; Weeber et al., 2005, 2007), compression (Glasser and Campbell, 1999), bubble acoustic (Hollman et al., 2007). More recently *in vivo* measurements, using Brillouin light scattering, have been added to the body of literature (Besner et al., 2016). The different principles adopted by various measuring techniques have produced a range of material findings. Results have shown that biomechanical properties vary between *in*

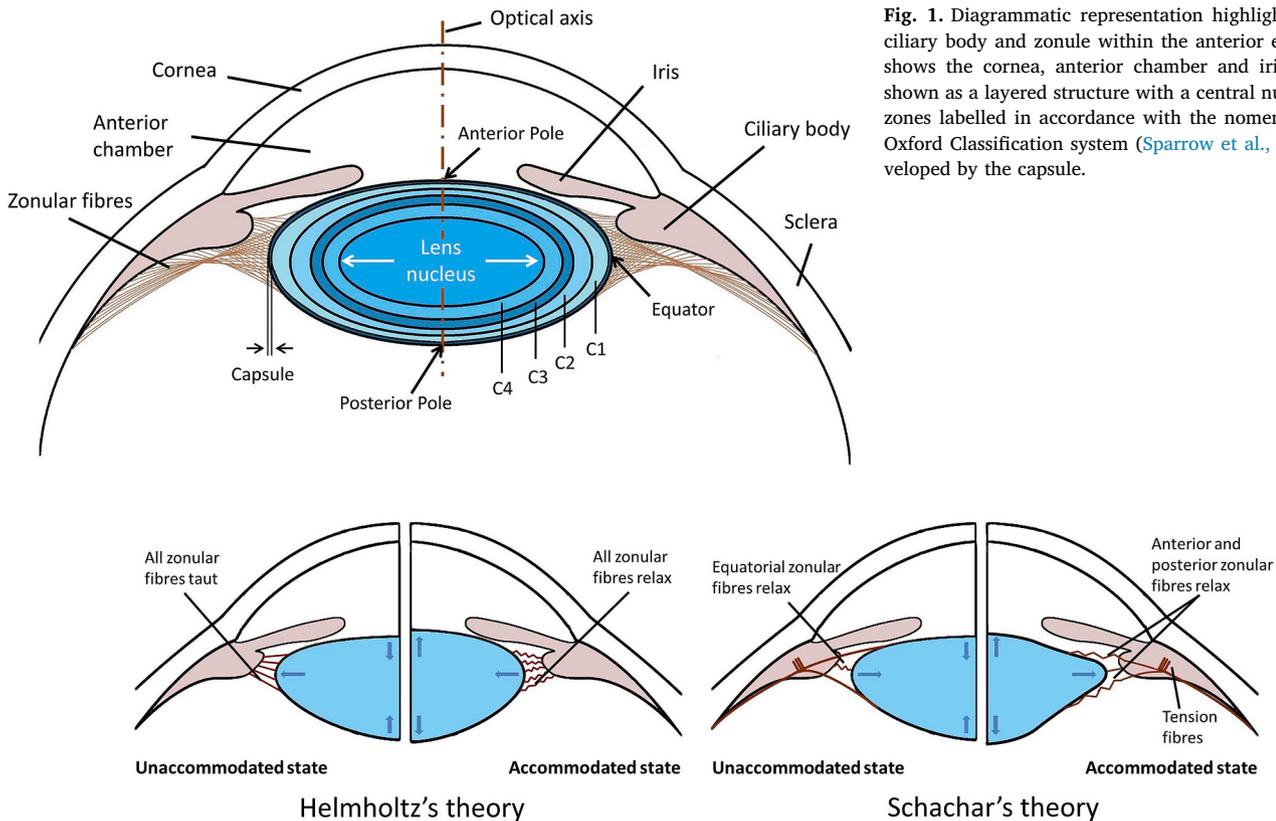


Fig. 1. Diagrammatic representation highlighting the lens, ciliary body and zonule within the anterior eye which also shows the cornea, anterior chamber and iris. The lens is shown as a layered structure with a central nucleus, cortical zones labelled in accordance with the nomenclature of the Oxford Classification system (Sparrow et al., 1986) and enveloped by the capsule.

Fig. 2. Schematic depiction of the accommodative theories of Helmholtz (1855) and Schachar (1994).

1994). As accommodative effort is reduced, the equatorial zonule becomes less tense (though not entirely relaxed), as tension in the anterior and posterior zonular fibres increases, causing the curvature in the central region to decrease (Fig. 2b).

1.2. Overview of current understanding of lens biomechanics

The lens needs to be transparent for the purposes of refraction and sufficiently pliable to fulfil changing visual demands. Such an optomechanical synchrony requires a well-aligned structure of lens fibres (Bron and Tripathi, 1998). A knowledge of the lenticular biomechanical response and how this relates to optical characteristics is not only essential for understanding the physiological process of accommodation and the development of presbyopia, but also of vital importance in the design of successful accommodative intraocular implants that can replicate the image quality of the eye lens (Küchle et al., 2002). The relationship between optical properties and the crystallin proteins, their relative concentrations, distributions and interactions between different protein classes and water (Brown et al., 1998; Lahm et al., 1985; Pierscionek and Regini, 2012), has been described in a linear mathematical relationship (Barer and Joseph, 1954); no such relationship has yet been defined between structural components and lens biomechanics.

dividuals, alter with age (Fisher, 1971; Heys et al., 2004; Weeber et al., 2007; Wilde et al., 2012) and are dependent on the measurement techniques used. Some of these techniques have been applied to measure the stiffness of the overall lens (Fisher, 1971; Glasser and Campbell, 1999) while others were applied to obtain localised measurements giving spatially varying descriptions of lens biomechanics (Besner et al., 2016; Heys et al., 2004; Weeber et al., 2007). The biomechanics of the capsule and zonule have undergone fewer investigations than the lens but are of significant importance for understanding the process of accommodation, the gradual loss of this function with age and the underlying structure/function relationships that provide image quality and focussing flexibility for a substantial part of the human life span.

2. Mechanical concepts and biomaterials

Biomechanics as a field of study applies the knowledge of engineering mechanics to motion and deformation problems in biology and physiology (Özkaya et al., 2016). The ability of the human lens to change its focus is a manifestation of the biomechanical capacity of the lens and associated components, the zonule and ciliary muscle. This section introduces mechanical concepts that describe the properties of biological materials.

2.1. Hooke's law

When an elastic body is stretched or compressed by a small distance, u , under a tensional or compressional force, F , the relationship between force and distance is described by Hooke's law:

$$F = ku \quad (1)$$

The constant, k , represents the stiffness of the elastic body and can be obtained by calculating the slope of a load-deformation (Knudson, 2007; Özkaya et al., 2016). Stiffness is a measure of the elasticity of the material and its reciprocal (distance/force) is termed compliance. A relatively flexible body, such as the human lens, has low stiffness but high compliance.

2.2. Stress and strain

Stress and strain are used to describe the behaviour of a material independent of its geometry. Stress is defined as load per unit area and is given in Pascals (Pa) or Newton/metre²; strain as extension per unit length and is unitless. A material under complex loading conditions encounters stress and strain in both normal and shear directions. A rod made of a homogenous material and with a uniform cross-sectional area, A , and a length, L , will have a change in length, ΔL when a uni-axial load, F , is applied. The normal stress, σ , and the normal strain, ϵ , are defined as:

$$\sigma = F/A \quad (2)$$

$$\epsilon = \Delta L/L \quad (3)$$

The definitions of shear stress, τ , and shear strain, γ , are slightly different from normal stress and strain with respect to their directions, as shown in Fig. 3.

$$\tau = F/A \quad (4)$$

$$\gamma = x/L \quad (5)$$

2.3. Young's and shear moduli

For an elastic material under small deformation, stress and strain have a linear relationship, described by the following equation:

$$\sigma = E\epsilon \quad (6)$$

$$\tau = G\gamma \quad (7)$$

The constant of proportionality, E is the ratio between normal stress σ and normal strain ϵ is called Young's modulus and is often simply referred to as the elastic modulus. The constant between the shear stress and shear strain, G , is called shear modulus or the modulus of rigidity. Young's modulus is a measure of the resistance to elastic deformation under load in the normal direction while shear modulus describes the tendency of a material to deform in the direction parallel to the applied

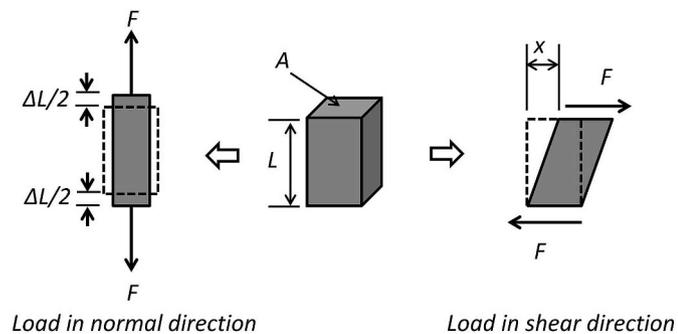


Fig. 3. Definitions of stress and strain in normal and shear directions where F is the load, L is the original length, A is the cross-sectional area, ΔL is the change in length and x is the shear deformation.

force. A stiffer material has a higher modulus and will undergo less deformation, under the same elastic load, than will a more pliable material. Linear elastic materials have constant values of Young's and shear moduli whilst for nonlinear materials these are functions of strain.

2.4. Poisson's ratio

Young's and shear moduli can be linked by a linear equation:

$$E = 2G(1 + \nu) \quad (8)$$

where ν is Poisson's ratio. It defines the ratio between strain in the transverse direction to strain in the axial direction and is a constant when the stresses are under the infinitesimal limit. For a material like the human lens, which is considered to be almost incompressible, Poisson's ratio approaches 0.5 (Hermans et al., 2009; Koretz and Handelman, 1983). This results in a magnitude of Young's modulus that is approximately three times that of the shear modulus ($E \sim 3G$).

2.5. Bulk and longitudinal moduli

Recent Brillouin scattering analyses reported the mechanical properties of lens substance in the form of bulk and longitudinal moduli (Bailey et al., 2010; Besner et al., 2016). The bulk modulus is a measure of volumetric elasticity. It is defined as the ratio between volumetric stress to volumetric strain for a unit volume under uniform loads in all directions (Fig. 4). The longitudinal modulus is defined as the ratio of axial stress to axial strain when strains in all other directions are equal to zero (Fig. 4). For a homogenous material, the relations between bulk modulus, K , longitudinal modulus, M , and Young's modulus, E , are:

$$K = E/3(1 - 2\nu) \quad (9)$$

$$M = E(1 - \nu)/(1 + \nu)(1 - 2\nu) \quad (10)$$

The lens ($\nu \sim 0.5$) has very high bulk and longitudinal moduli. The term $(1 - 2\nu)$ renders the conversion of Young's modulus to bulk or longitudinal moduli, highly sensitive to very small variations in Poisson's ratio when it approaches 0.5 (Mott et al., 2008).

The relation between the bulk and longitudinal moduli is described by:

$$K = M(1 + \nu)/3(1 - \nu) \quad (11)$$

with $\nu \sim 0.5$, the $K \sim M$. Studies reporting these two forms of moduli can be directly compared (Bailey et al., 2010; Besner et al., 2016; Scarcelli and Yun, 2012).

2.6. Homogeneity and isotropy

The study of biological tissue and materials needs to consider the concepts of homogeneity and isotropy. Homogeneity describes the mechanical properties of a material that are the same at all points. An isotropic material exhibits the same mechanical properties in all directions at a given point. Biological tissue is composed of several different constituents and manifests inhomogeneous and anisotropic behaviour (Brown et al., 1998). To date, nearly all mechanical testing of the lens has assumed isotropy (with the exception of Koretz and Handelman, 1983 and Reilly and Ravi, 2009), whilst many evaluations have been of inhomogeneity (summarised below).

2.7. Elasticity

Elasticity is defined as the ability of a material to resume to its original stress-free size and shape upon removal of applied loads (Özkaya et al., 2016). For an ideal elastic material, the unloading stress-strain curve follows exactly the same path as the loading curve, shown in Fig. 5a and b. The properties of elastic materials are independent of

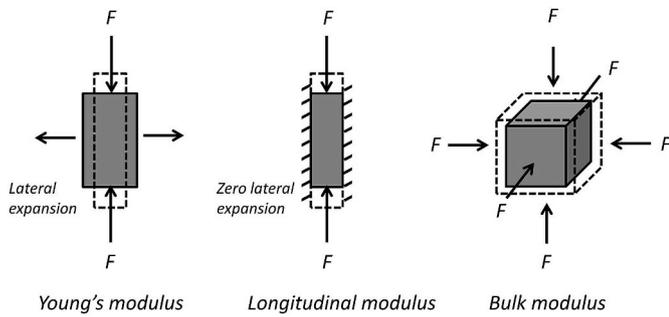


Fig. 4. Diagrammatic illustration of how Young's modulus, longitudinal modulus and bulk modulus are measured showing directions of load (F) and of expansion.

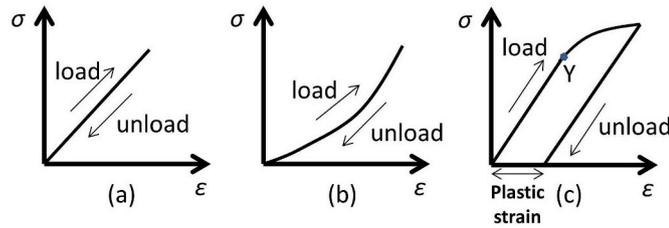


Fig. 5. Examples of loading and unloading curves of (a) a linear elastic model (b) a non-linear elastic model and (c) a plastic model. (ϵ is the strain, σ is the stress).

the loading rate. If the stress response is linearly related to the strain, the material is a linear elastic material (Fig. 5a); otherwise it is a nonlinear elastic material (Fig. 5b). Biological soft tissues, are usually nonlinear elastic materials but will deform linearly under small strains.

2.8. Plasticity

Plasticity implies permanent deformation (Özkaya et al., 2016). The elasticity of a material holds only up to a limit point, called the yield point (Y in Fig. 5c), beyond which the slopes of the stress-strain curve decrease rapidly (Brown et al., 1998). The stress corresponding to the yield point is the upper limit of the stress that can be applied to the material without causing any permanent (plastic) deformation. Beyond the yield point, the unloading curve will no longer be the same path as the loading curve (Özkaya et al., 2016). The portion of the curve beyond the yield limit is called the plastic region (Brown et al., 1998; Özkaya et al., 2016). When the load is removed, only the elastic deformation is reversed with the plastic portion causing permanent deformation (Fig. 5c). Plastic materials are used for intraocular implants.

2.9. Viscoelasticity

A viscoelastic material has characteristics of both elasticity and viscosity: the deformation is reversible and the stress-strain responses are dependent on time and on the rate of loading (Knudson, 2007). The loading and unloading paths of a typical viscoelastic stress-strain curve do not coincide but form a hysteresis loop (Fig. 6a). The area enclosed by the loading and unloading curves is the energy lost during the loading process and is dependent on the rate of loading applied to deform the body (Brown et al., 1998; Özkaya et al., 2016). Two typical phenomena demonstrated by viscoelastic materials are creep and relaxation (Fig. 6b and c). Creep refers to increasing strain over time for a material under a constant stress; relaxation is the gradual decrease in stress when a material is under constant strain (Brown et al., 1998; Knudson, 2007).

Two common empirical viscoelastic models: Maxwell and Voigt, that are applied to biological systems are shown in Fig. 7. They

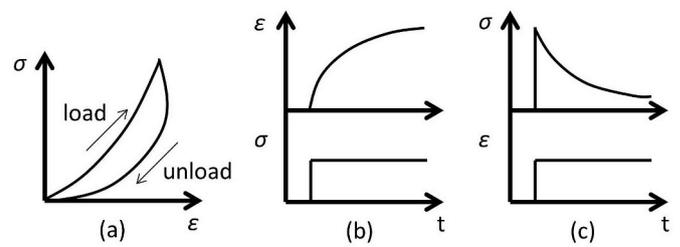


Fig. 6. (a) Examples of a) loading and unloading curves of a viscoelastic model (b) creep and (c) relaxation behaviour of a typical viscoelastic material. (ϵ is the strain, σ is the stress and t is the time).

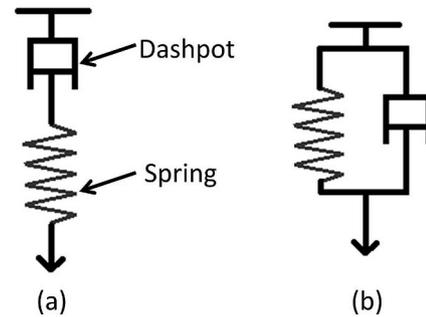


Fig. 7. Diagrammatic representation showing the components of (a) the Maxwell model and (b) the Voigt model.

comprise a spring, to simulate the elastic behaviour, and a dashpot, to simulate viscous behaviour (Fung and Tong, 2001). The response of a spring can be described by equation (1), that of a dashpot by equation (12), ie that the rate of displacement, du/dt , is proportional to the applied load (Özkaya et al., 2016).

$$F = \eta du/dt \tag{12}$$

where η is viscosity of the dashpot.

The Maxwell model comprises a spring in series with a dashpot, such that a stress applied to the entire system is equally applied to both the spring and the dashpot while the resultant total strain is a sum of the strains in both the spring and the dashpot (Brown et al., 1998; Fung and Tong, 2001; Özkaya et al., 2016). The Voigt model is comprised of a spring in parallel with a dashpot so that a stress applied to the entire system is shared by the spring and the dashpot while the resultant strains in both parts are equal to the total strain (Brown et al., 1998; Fung and Tong, 2001; Özkaya et al., 2016).

The Maxwell and Voigt models can be used in combination to represent the viscoelastic behaviour of a number of biological materials such as cartilage, white blood cell membranes (Brown et al., 1998; Fung and Tong, 2001; Özkaya et al., 2016) as well as the eye lens together with surrounding components: the zonule, ciliary muscle and choroid (Beers and Van Der Heijde, 1994, 1996; Ejiri et al., 1969).

2.10. Poroelasticity

The three aforementioned material properties illustrate the mechanical response of ideal materials and have been used in modelling of lens behaviour. Other, less common properties, have also been applied to investigations of lens biomechanics. Poroelasticity, describes the interaction between the flow of incompressible fluid and the structural deformation of a compressible elastic solid within a porous medium. The deformation of the solid induces fluid flow which in turn interacts with the structural deformation. Using a constitutive model that treats the lens as a poroelastic material, Burd and Wilde (2016) considered the flow of fluid and local volume change to model the surgical process of laser lentotomy.

2.11. Summary

The material properties and mechanical concepts described have all been applied to or measured on the lens and/or other components of the accommodative system. These studies, detailed in subsequent sections, have sought to understand: changes with age, the contribution of these changes to the loss of accommodation, the opto-mechanical relationship and/or values of material parameters needed for testing lens models.

3. Measurement techniques

3.1. The lens

The various approaches developed to map the spatially varying distribution of elastic moduli across the lens (Bailey et al., 2010; Heys et al., 2004; Hollman et al., 2007; Wilde et al., 2012) can be classified into two groups: elastic measurements taken on lenses in quasi-static states (Bailey et al., 2010; Heys et al., 2004, 2007; Hollman et al., 2007) and dynamic measurements taken with oscillatory deformations applied to lenses at different frequencies (Itoi et al., 1965; Weeber et al., 2005, 2007). These dual approaches are reviewed below.

3.1.1. Elastic measurements

3.1.1.1. Spinning. The spinning lens method was an early measurement approach originally developed by Fisher (1971). The lens was rotated around its central axis at a fixed speed such that the induced centrifugal forces deformed it in a manner that was intended to mimic the lens shape change during accommodation. The profile of the spinning lens was monitored by a camera, which captured changes in the sagittal thickness and in the equatorial diameter. These parameters, together with the density of the lens, were used to calculate Young's modulus for both the nucleus, determined from a central spherical region with a radius equal to the anterior thickness of the lens (Fisher, 1971), and the cortex. This method has the advantage of keeping the lens intact. It can also be extended to estimate the zonular forces (Fisher, 1977, 1986) (reviewed later). Subsequent work by Burd et al. (2006), indicated that Fisher's work relied on several geometric and mechanical simplifying assumptions and that contributions of capsular elasticity were included in the calculations. Burd et al. (2006) suggested that this could have resulted in a potential error that led to the result of a higher cortical than nuclear elastic modulus. A more recent study that also applied the spinning technique by Wilde et al. (2012) excluded the capsular elasticity by applying centrifugal forces to decapsulated lenses. The lack of a capsule may have caused some dehydration to the lens outer layers during the spinning process; the influence of this on the results is not known. Unlike Fisher (1971), who calculated Young's modulus, Wilde et al. (2012) combined experimental data with computational analysis, to determine the shear modulus of the lens.

3.1.1.2. Indentation. Shear modulus has been measured using indentations, with a custom-made probe, on the equatorial plane of a sectioned lens (Heys et al., 2004, 2007). The shear modulus can be determined from equation (13) (Heys et al., 2004):

$$P = 4RdG/(1 - \nu) \quad (13)$$

where P and d are the total load and recorded maximal depth of indentation respectively and R is the radius of the cylindrical probe. Indentation provides a means of localised measurement that demonstrates biomechanical differences across the equatorial plane. The sectioning procedure, and freeze/thawing of samples (Heys et al., 2004) are shortcomings of the measurement. Changes to lens hydration, and whether the extent of this can differ with age of the cells and the free and bound water ratios, which also vary with age (Lahm et al., 1985) have not been estimated.

3.1.1.3. Bubble-based acoustic radiation force. This measurement requires the lens to be enclosed in collagenous gelatin with ultrasound access from the top and laser access from the bottom (Erpelding et al., 2007; Hollman et al., 2007). The laser creates micro-bubbles within the lens tissue at 1 mm intervals from the lens centre to the lens periphery and the ultrasound transducer applies an acoustic radiation force to the bubbles, tracking their resultant displacements. The displacement of each bubble is proportional to the local compliance of the lens substance from which a spatially varying Young's moduli can be determined using a constant of proportionality and the inverse of the displacements of bubbles at different locations (Erpelding et al., 2007; Hollman et al., 2007). Bubble-based acoustic radiation has the potential to be performed *in vivo*.

3.1.1.4. Compression. The compression method is only applicable for determining overall mechanical behaviour of the lens as it requires a squeezing of the intact body. An early compression study using a mechano-electric transducer to determine elasticity of rabbit and cat lenses (Kikkawa and Sato, 1963), a subsequent study adopting a pressure transducer on human lenses (Glasser and Campbell, 1999) as well as murine lenses (Baradia et al., 2010; Fudge et al., 2011; Gokhin et al., 2012) all reported resistance of the lens to external deformation. These methods were limited because of the complexity in converting the measured parameters into elastic moduli, as this requires consideration of lens shape as well as the contact area between the compressor and the lens. A more recent study, that adopted an inverse FE model to determine the shear moduli of a porcine and a murine lens, by scanning a range of values to find the optimum match between the FE model and experimental measures, was reported by Reilly and Cleaver (2017). Further investigations are needed to improve this technique if it is to produce more accurate and comparable measures of lenticular elasticity. The compression and indentation tests, with loads applied at higher frequencies, could also be used to characterise the dynamic behaviour of lens material.

3.1.1.5. Brillouin Light Scattering analysis. Brillouin Light Scattering (BLS) is a type of inelastic scattering that makes use of two interactions between optics and acoustics: acoustic wave modulation of optical photons and the optical field inducement of acoustic waves (Bailey et al., 2010). In more detail, the propagation of acoustic waves can spatially and temporally modulate material density by creating expansions and contractions of the medium. The refractive index of the medium is related to density; periodic modulation of refractive index scatters light (Besner et al., 2016). Conversely, incident light can initiate acoustic waves from the material by creating spatial and temporal variations in elastic strains (Bailey et al., 2010). These two interacting mechanisms cause the incident light to either gain energy from existing acoustic waves in a medium, associated with upshift frequency (anti-Stokes scattering) or to transfer energy to the material to induce acoustic waves, associated with downshift frequency (Stokes scattering). Hence, it is possible to determine the elastic properties of a medium using BLS by monitoring the Brillouin frequency shift, as this is linked with the mechanical properties of the material (Besner et al., 2016).

This method, applied to human lenses by Scarcelli and Yun (2012) and Besner et al. (2016), is currently the only method for measuring biomechanical properties of the lens that has been conducted *in vivo*. It is superior to other approaches as it provides non-destructive measurements that are suitable for characterizing spatial variations of lens mechanical properties with high resolution (Bailey et al., 2010). The technique measures the compressive moduli: bulk modulus K (Bailey et al., 2010) and longitudinal modulus M (Besner et al., 2016) rather than the Young's or shear moduli. Compressive moduli are described by the following formulae:

$$K = \rho\lambda^2f^2/4n^2 \quad (14)$$

$$M = \rho f^2 \lambda^2 / \left(4n^2 \sin^2 \left(\frac{\theta}{2} \right) \right) \quad (15)$$

where ρ is the density of the medium, λ is the wavelength of the incident laser light, f is the average of Stokes and anti-Stokes frequency shift, n is the refractive index of the medium and θ is the angle between the incident and scattered light. It should be noted that [Besner et al. \(2016\)](#) used a constant value of 0.5636 g/cm^3 for the ratio, ρ/n^2 , (in equation (15)) and that this was verified on *in vitro* porcine lenses ([Scarcelli et al., 2011](#)). How this may compare to variations in density (ρ) and refractive index (n) across human lenses, the refractive index profiles of which are not parabolic (reviewed in [Pierscionek and Regini, 2012](#)) and vary with age was not taken into account.

3.1.1.6. Optical Coherence Elastography. Optical Coherence Elastography (OCE) has been used to measure Young's moduli of *in situ* rabbit lenses ([Wu et al., 2015](#)). The principle of elastography (reviewed by [Wang and Larin, 2015](#)), is a correlation between the tissue elasticity and deformation caused by external mechanical excitation, ie acoustic radiation ([Wu et al., 2015](#)) and air puffs ([Wu et al., 2016](#)). The lens displacement was fitted to mechanical models in order to calculate the average Young's modulus ([Wu et al., 2016](#)). If this measurement were to be undertaken on an intact eyeball, remote loading (to take account of the cornea) would be required ([Wu et al., 2015](#)).

3.1.2. Dynamic measurements

The methods described in the previous section concerned measurement of elastic properties of lenses in the quasi-static state ie the observation time scale was in minutes or hours ([Itoi et al., 1965](#)). The lens, however, exhibits viscoelastic behaviour when exposed to different rates of loading ([Beers and Van Der Heijde, 1994](#); [Glasser and Campbell, 1999](#); [Kikkawa and Sato, 1963](#); [Itoi et al., 1965](#)). This is believed to arise because of coupling between the lens fibre cell membrane and cytoskeleton ([Alcala and Maisel, 1985](#); [Beers and Van Der Heijde, 1994](#)) as well as the cytoplasmic movement. Therefore it cannot be completely described using a single elastic modulus. In addition to studies on intact lenses, consideration has been given to the biomechanical characteristics of crystallin protein solutions ([Tiffany and Koretz, 2002](#); [Reilly et al., 2008](#)). These studies demonstrated a shear-thinning effect of these solutions and confirmed that the cytosol has non-Newtonian characteristics suggesting that this imparts a stability to the lens structural order during the accommodative process. It has been shown that *in vitro* lenses deform rapidly in response to compression but recover slowly after unloading ([Itoi et al., 1965](#); [Kikkawa and Sato, 1963](#)). The dynamics of accommodation also change with age ([Beers and Van der Heijde, 1996](#)) and viscoelastic behaviour of the lens is dependent on frequencies used in the measurement ([Weeber et al., 2005](#)).

3.1.2.1. Dynamic Mechanical Analysis. The general principle for performing Dynamic Mechanical Analysis (DMA) requires subjecting the lens to oscillatory deformation at different frequencies, either in normal or shear directions. The relation between the oscillatory force and deformation provides information about both elasticity and viscosity. This dynamic mechanical analysis has been applied to intact lenses ([Weeber et al., 2005](#)), lens slices ([Schachar et al., 2007](#); [2011](#)), protein solutions ([Tiffany and Koretz, 2002](#); [Reilly et al., 2008](#)) and bisected lenses ([Weeber et al., 2007](#)). The applied displacement $x^*(t) = x_0 e^{i\omega t}$ and the reaction force $F^*(t) = F_0 e^{i(\omega t + \delta)}$ will have the same frequency but a phase difference δ . The measured force divided by the applied displacement represents the complex spring constant. The essential step in converting the complex spring constant into a complex modulus, ie complex shear modulus G^* , of the measured lens sample needs to take account of the lens shape. The complex shear modulus $G^* = G' + iG''$ consists of a real part G' , called the storage shear

modulus, for characterising the elastic properties and an imaginary part G'' , called the loss shear modulus, for characterising the viscous properties. A very early study by [Itoi et al. \(1965\)](#) applied oscillatory compressions on an 85-year-old human lens sandwiched between two dishes and used mathematical analysis to approximate the lens to a cylinder of equivalent length to the lens thickness and a cross-sectional area equal to the surface area of the dishes used in the measurements. The apparent Young's modulus of the lens was found to increase slightly with age between 10^4 to 10^5 Pa with oscillatory frequency. More recently, dynamic oscillatory indentation was applied to different locations on sectioned lens samples and computational modelling used to take account of the lens shape when converting measurements of force-displacement into shear modulus values ([Weeber et al., 2007](#)).

3.1.2.2. Biomechanical model. [Beers and van der Heijde \(1994, 1996\)](#) applied a Voigt model to describe the human accommodative apparatus. The idea of representing the lens with a Voigt model had been suggested previously by [Ejiri et al. \(1969\)](#) to describe the dynamic behaviour of canine and feline lenses. The Voigt model used by [Beers and van der Heijde \(1994, 1996\)](#), in series with three springs of different spring constants representing the peripheral and axial zonular fibres and choroid, is shown in [Fig. 8](#). [Beers and Van Der Heijde \(1994, 1996\)](#) measured the *in vivo* responses of accommodative process in healthy human subjects and fitted those responses to the model to calculate the two time-constants describing the far-to-near and near-to-far responses. The far-to-near dynamics are determined by the viscoelastic properties of the lens, near-to-far dynamics are dependent on the properties of the lens as well as on the elasticity of the zonular fibres and the choroid. The two time-constants were then used to calculate ratios that could predict the dynamics of accommodation.

3.2. The capsule

Knowledge of capsular biomechanics is also important for understanding the stabilising influences on intraocular implant lenses. Three approaches: inflation, uniaxial stretching and atomic force microscopy, have been employed to determine the biomechanical properties of the capsule.

3.2.1. Inflation

The inflation test designed by [Fisher \(1969\)](#) included two chambers filled with isotonic saline, with controlled pressure between the two chambers. A glass plate with a central hole clamping a disc of anterior lens capsule was placed between the two chambers and the pressure in the lower chamber was increased to deform the lens capsule to an upward facing spherical cap. Young's modulus was determined from the applied pressure and the induced volume of the capsular disc. This inflation test was later repeated by [Danielsen \(2004\)](#) and in both studies the capsule was treated as an isotropic material.

A more advanced design of inflation test by [Pedrigi et al. \(2007\)](#) was

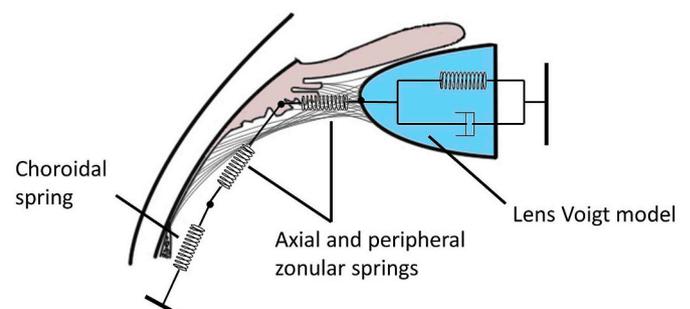


Fig. 8. The biomechanical model of [Beers and Van Der Heijde \(1994, 1996\)](#) consisting of springs and a dashpot.

used to characterise the regional multiaxial behaviour of the anterior lens capsule. Pressure was applied to the anterior capsule by injecting fluid to separate the capsule from the lens; a number of video tracking markers were arranged on the exposed capsule. The relationship between the applied pressure and locations of the markers were fitted using the Fung exponential model that is used to describe bio-membrane behaviours (Fung, 1990). The coefficients determined from this model include the overall stiffness of measured capsule as well as the capsular stiffness in circumferential and meridional directions (Pedrigo et al., 2007). However, Burd and Regueiro (2015) showed that this apparent anisotropy was the result of application of an unsuitable constitutive description of the lens capsule.

3.2.2. Uniaxial stretching

Krag et al. (1997) and Krag and Andreassen (2003a) uniaxially stretched anterior and posterior capsular samples at a constant speed, monitoring elongation and force until the tissue ruptured. The mechanical behaviour of the capsule within the entire range of strains from zero to the rupture point was recorded and the nonlinear stress-strain response of the lens capsule was determined for various ages. The capsule exhibits nonlinear elasticity when large strains are induced during uniaxial stretching (Krag and Andreassen, 2003b). However, Hermans et al. (2009) showed that the capsular strain during accommodation is much lower than this limit, with the surface area of unaccommodated lens capsule, on average, only 5% higher than that for the accommodated lens capsule. The elastic properties within the linear range, usually less than 10% strain, are of major relevance. It should also be noted that the lens capsule has a much higher stiffness than the lens substance; capsular Young's modulus was found to be of the order of MPa (megapascal) compared to Young's modulus of the lens which is in kPa (kilopascal).

3.2.3. Atomic Force Microscopy

Atomic Force Microscopy (AFM) has been used to investigate morphological and mechanical properties of biological cells and materials at nanometre-scale resolution (Last et al., 2010; Ziebarth et al., 2011). This technique, in contrast to inflation and stretching methods, can measure local moduli and indicate any heterogeneities. The AFM cantilever scans across the sample surface, its deflection measured with a laser and the cantilever and topological height changes of the sample surface are recorded. The reaction force, at a single point, is calculated by multiplying the spring constant of the cantilever by the amount of its deflection. The elastic moduli of the sample are found by fitting the force/deflection curve to models that describe various biomechanical behaviours (Last et al., 2010; Tsaousis et al., 2014; Ziebarth et al., 2011).

Table 1
Summary of measuring methods.

	Methods	Static	Dynamic	<i>in-vivo</i>	<i>in-vitro</i>	Spatially varying	Type of modulus
Lens	Spinning	✓			✓		Young's, Shear
	Indentation	✓	✓		✓	✓	Shear
	Compression	✓	✓		✓		–
	Bubble-acoustic	✓			✓	✓	Young's
	BLS	✓		✓	✓	✓	Longitudinal Bulk
	OCE	✓			✓		Young's
	DMA Biomechanical model		✓ ✓		✓ ✓	✓	Shear –
Capsule	Inflation	✓			✓		Young's
	Stretching	✓			✓		Young's
	AFM	✓			✓	✓	Young's
Zonules	Stretching	✓			✓		Young's

3.3. The zonule

The zonule, as a complex of fine ligaments with thin cylindrical forms and uniform cross-sectional areas, can only withstand forces of tension. Young's modulus of zonular fibres has been measured using a uniaxial stretching test, with stress determined by dividing the applied stretching force F by the cross-sectional area A (equation (2)) and strain taken as the ratio between the elongation ΔL and the original length L (equation (3)). Currently no technique allows direct measurement of the *in vivo* zonular force. Young's modulus has been measured by uniaxial stretching (Michael et al., 2012; Van Alphen and Graebel, 1991) using cross-sectional area values obtained from the literature (Kaczurowski 1964; Weeber and van der Heijde, 2008). It has been pointed out by Cortés et al. (2015) that radial cuts are necessary in stretching tests to avoid circumferential tensions from developing in the ciliary body.

3.4. Summary

The range of methods used to measure the biomechanical properties of the lens and associated components involved in accommodation, as well as the type of modulus obtained from each method, is given in Table 1. Given this diversity, that results vary so widely is not unexpected. In addition, the states and measurements of sample tissue are not consistent, *post-mortem* lenses are in different states: fresh or thawed, some measurements are made in localised regions of the lens, some on bisected samples, others on the whole lens. This renders it difficult to make direct comparisons. The range of different material properties need to be properly interpreted and collated for the collective knowledge to provide a more complete understanding of the process of accommodation and changes with ageing.

4. Material properties: changes with age and implications for treatment

4.1. The lens

The interest in biomechanics of the lens and component tissues involved in accommodation is largely to gain an improved degree of discernment about the contribution of each tissue to this process and, ultimately, to understand the only physiological change in this optical system with age: the loss of function that is known as presbyopia. (The only other age-related change in the lens, senile cataract, is linked with pathological processes). From the range of methods employed to measure biomechanics of the components involved in accommodation, age-related trends can be compared. Such comparison may offer insights, albeit incremental, into the role of biomechanics in accommodation and

the causal factors that lead to presbyopia.

4.1.1. The material properties of the nucleus and the cortex

The seminal study by Fisher (1971), which measured human lenses aged from 4 months to 67 years, reported a higher Young's modulus in the cortex, ranging from 0.5 kPa to 4.0 kPa, than in the nucleus, where values ranged from 0.5 kPa to 3.5 kPa. In both parts of the lens, Young's moduli increased continuously throughout the lifespan, with a greater rate of change seen in the cortex than in the nucleus up to around 40 years of age and a rapid increase in nuclear modulus thereafter. This yielded the interesting result that the nuclear modulus was lower than the cortical suggesting that the former was the more pliable. Wilde et al. (2012) measured twenty-nine human lenses, aged from 12 years to 58 years, and found that the shear modulus in the nucleus is lower than that of the cortex in the young lens but that the change in nuclear shear modulus occurs at a faster rate, with age, than the change in cortical shear modulus. Hence, shear modulus of the nucleus becomes higher than that of the cortex at around 45 years of age, after which the cortical shear modulus shows a slightly decreasing trend. The indentation method applied by Heys et al. (2004), on eighteen *post-mortem* lenses aged from 14 to 78 years, treated measurements taken at the lens centre and at the lens periphery as representative for the entire nucleus and cortex respectively. The shear moduli, in both the nucleus and the cortex, were found to increase continuously with age: the cortical shear modulus increases approximately 53 fold from 48.5Pa (in a 14-year-old lens) to 2577Pa (in a 76-year-old lens) while the nuclear shear modulus demonstrated a more pronounced increase of 930 fold from 25.7Pa (in a 20-year-old lens) to 23954Pa (in a 73-year-old lens). The crossover age, at which the moduli of the nucleus become higher than that of the cortex, was found to be around 30–35 years of age (Heys et al., 2004).

A BLS analysis, on twenty-nine intact *post-mortem* capsulated human lenses, aged from 30 to 70 years, measuring bulk modulus was conducted by Bailey et al. (2010). Converting bulk to Young's modulus requires a value of Poisson's ratio to which the results are very sensitive given that Poisson's ratio is in denominator (equation (9)). Yet, no study to date, has measured the value of Poisson's ratio of the lens and, given the sensitivity of this, any conversion would incur high degrees of inaccuracy that rise by orders of magnitude with fractional increments in the value of this important factor. Bailey et al. (2010) reported that the bulk modulus of the nucleus at 2.79 ± 0.14 GPa, was larger than that of the lens cortex, 2.36 ± 0.09 GPa, with no age dependency in either. A comparison of the mechanical moduli reported by these studies is shown in Fig. 9. Young's moduli, measured by Fisher (1971), are converted to shear moduli to allow a comparison with the findings of Wilde et al. (2012) and Heys et al. (2004).

Variations in the ageing trends of elastic moduli of the nucleus and the cortex could be attributed to several factors. The representative locations/regions of the lens nucleus and cortex measured by different

studies are not consistent; the disturbances to lens substance brought by handling procedures involved in sample preparation stages, ie thawing/sectioning. Additionally, the transition between free and bound water with age occurs at various rates in different regions of the lens, with the greatest changes found in the oldest parts of the lens, the nucleus (Lahm et al., 1985; Heys et al., 2008). This would manifest as a wider variation in the nuclear moduli when comparing fresh and frozen tissue (Heys et al., 2004); the different water states may cause the tissue to respond differently to the various measurement techniques. This may explain why the greatest variations were seen in the nuclear regions of the oldest lenses (Fisher, 1971; Heys et al., 2004; Wilde et al., 2012).

4.1.2. Spatially varying properties in the lens equatorial plane

The profiles of elastic moduli for two lenses, aged 19 years and 64 years, reported by Heys et al. (2004) using indentation, showed that the younger lens had a relatively uniform distribution of shear modulus (Fig. 10a) that ranged from 0.05 kPa to 0.08 kPa compared to the older lens. The shear modulus in the older lens increased from 2 kPa at the periphery to 18 kPa in the centre (Fig. 10e). This trend was also seen by Hollman et al. (2007) who found that Young's moduli in three lenses, aged 40–41 years, decreased from 5.2 kPa in the centre to 1.1 kPa at the periphery and from 10.6 kPa in the centre to 1.4 kPa at the periphery in nine lenses aged between 63 and 70 years (shown in Fig. 10c and e as shear modulus converted using $G = E/3$). Dynamic oscillatory indentation used by Weeber et al. (2007) on ten human lenses aged between 19 and 78 years also demonstrated that shear modulus increases with age at all measured positions across the equatorial plane. However, the rate of increase was found to be considerably greater with age in the lens centre, by a factor of 10^4 over the measured age range, compared to 10^2 at the periphery. The shear modulus at the lens centre is lower than in the periphery for young lenses aged below 40 years (Fig. 10b), becomes almost uniformly distributed for lenses between 40 and 50 years of age (Fig. 10d) and is higher than the periphery in older lenses aged above 55 years of age (Fig. 10f) (Weeber et al., 2007). Although the magnitudes of the moduli reported by these studies vary greatly, especially in older age (Fig. 10e and f), the spatial distributions of elastic moduli across the lens equatorial plane are relatively comparable within different age groups (Weeber et al., 2007).

4.1.3. Spatially varying properties along the lens optical axis

The only study that has measured biomechanical properties along the optic axes of lenses *in vivo* was conducted by Besner et al. (2016) using BLS. Fifty-six eyes from thirty healthy human subjects aged from 19 to 63 years were investigated and the longitudinal modulus, along the optic axis, was found to increase from the lens periphery to a central plateau at all ages. The width of this plateau region increases with age over the tested age range and there is a concomitant steepening of the cortical gradient (Besner et al., 2016). This mimics the trends seen in refractive index profiles with age (Pierscionek et al., 2015). No age dependence was found for the peak modulus magnitude across the central plateau in human lenses aged from 19 to 45 years but a slightly decreasing trend was observed in lenses aged from 45 to 64 years (Besner et al., 2016). Notwithstanding the similarities between these profiles (Besner et al., 2016) with those of refractive index from human lenses of comparable ages (Pierscionek et al., 2015), it should be noted that the latter study was on *in vitro* samples that were not under any zonular tension and therefore, to some degree, accommodated; the former study was undertaken on subjects whose lenses were in an unaccommodated state.

4.2. The lens capsule

The findings of Fisher (1969) suggested that Young's modulus in the anterior capsule in childhood is about 6 MPa and that this decreases to 3 MPa at around 60 years of age and further decreases to 1.5 MPa in extreme old age (Fig. 11a). Danielsen (2004), applying a similar

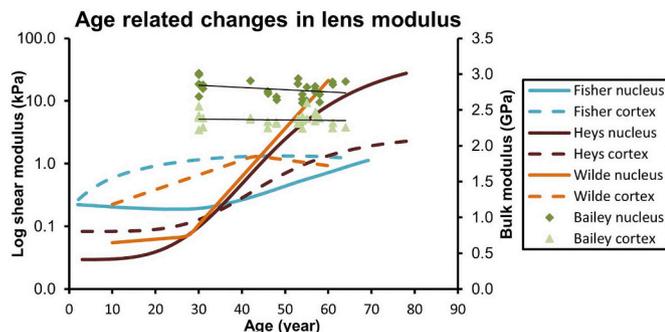


Fig. 9. Comparison of lens shear modulus (in kPa) in the nucleus and cortex with age taken from Fisher (1971), Heys et al. (2004), and Wilde et al. (2012) (Young's moduli from Fisher (1971) were converted to shear moduli using $G = E/3$), as well as bulk modulus (in GPa) taken from Bailey et al. (2010).

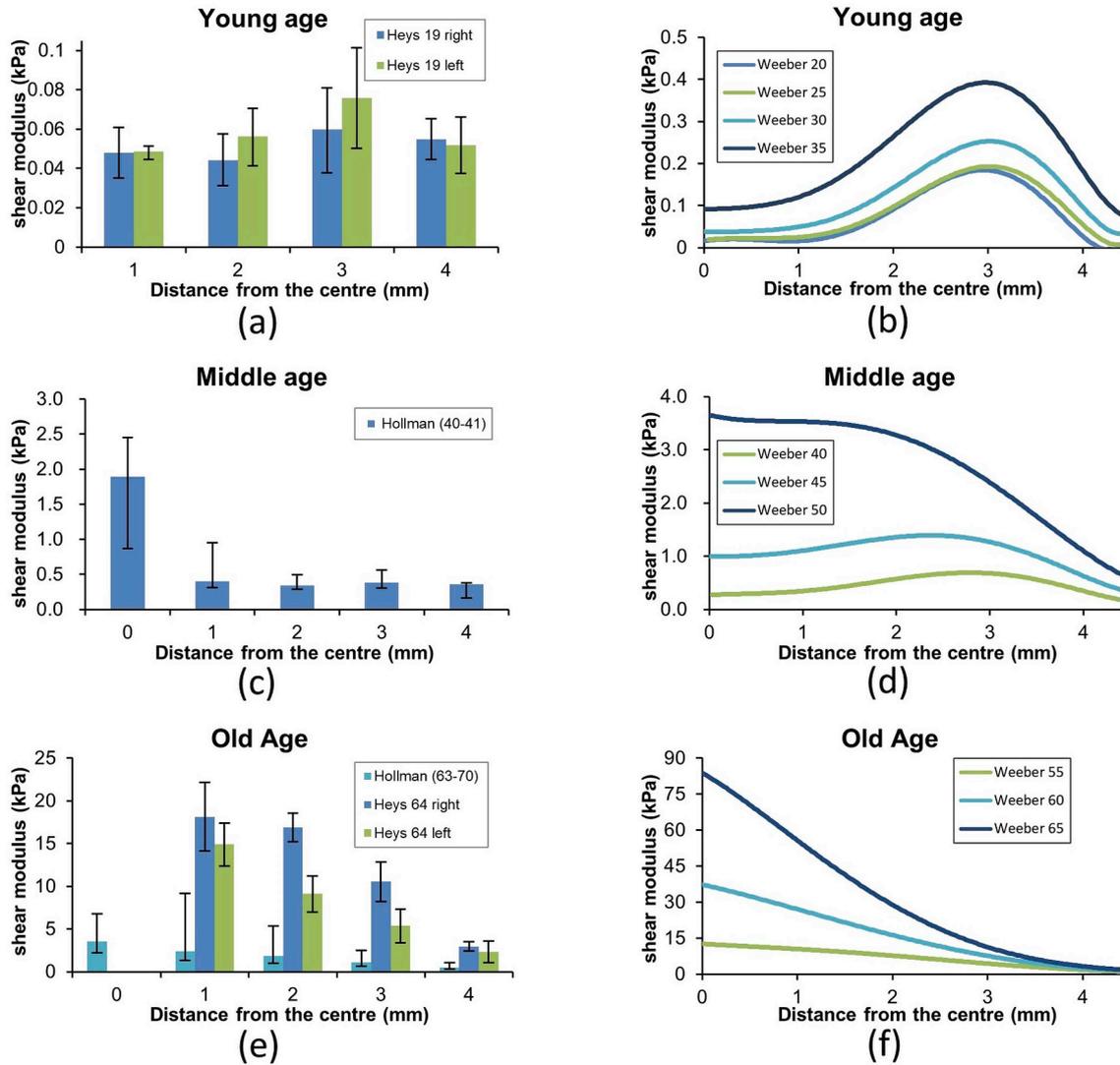


Fig. 10. Comparisons of shear moduli across the equatorial section reproduced from Heys et al. (2004), Hollman et al. (2007) and Weeber et al. (2007) for (a, b) lenses younger than 40 years of age, (c, d) lenses between 40 and 50 years of age and (e, f) lenses older than 55 years of age.

method as Fisher (1969), to anterior human lens capsules, found Young's modulus at 10% strain to be 2.40 MPa for lenses aged between 58 and 96 years. In these two studies (Danielsen, 2004; Fisher, 1969), the capsule was treated as an isotropic material. Pedrighi et al. (2007) demonstrated nonlinear and regionally anisotropic behaviour of the lens capsule for both normal and diabetic human lenses aged from 29 to 81 years old. The results suggested that, with progression towards equator, the stiffness of the lens capsule increases in the circumferential

direction and decreases in the meridional direction (Pedrighi et al., 2007). The lens capsule was modelled using a periodic hexagonal pattern that is more representative of the structural collagen arrangement than any other study to date (Burd, 2009; Burd and Regueiro, 2015). This approach yielded results comparable to those of Pedrighi et al. (2007) indicating that anisotropy, included in the Fung exponential model (Pedrighi et al., 2007) is not necessary for interpreting experimental results. Krag et al. (1997) and Krag and Andreassen (2003a)

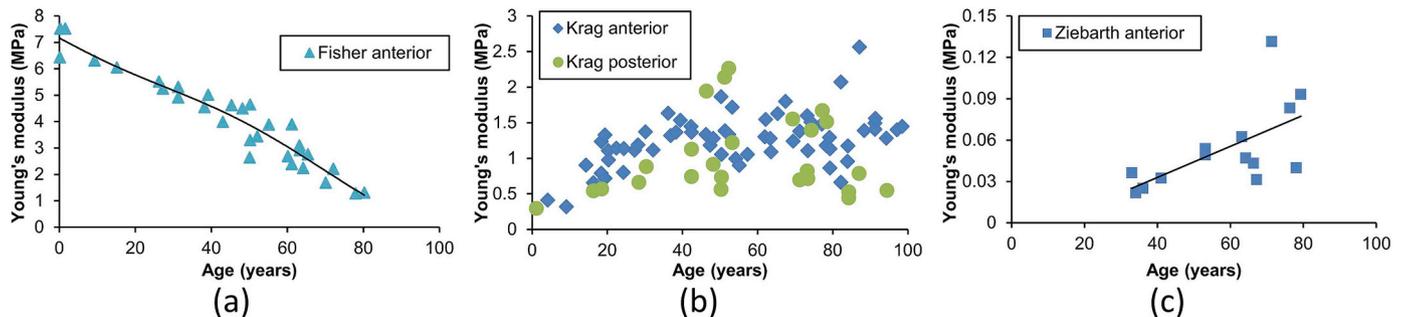


Fig. 11. Young's modulus of the lens capsule in MPa plotted against age in years, reproduced from (a) Fisher (1969), (b) Krag and Andreassen (2003a) and (c) Ziebarth et al. (2011).

examined both anterior and posterior capsular specimens from human lenses over a wide age range from birth until the tenth decade of life. Young's modulus for the posterior lens capsule was found to range from 0.3 MPa to 2.3 MPa, differing by 0.25 ± 0.1 MPa from the anterior lens capsule (reanalysed from Krag et al., 1997). Young's moduli of both anterior and posterior lens capsules increased from birth until middle age and decreased thereafter (Fig. 11b). The anterior capsular Young's modulus examined by Ziebarth et al. (2011) using AFM from lenses aged between 33 and 79 years old showed significant increases with age (Fig. 11c) from 20.1 kPa to 131 kPa but the magnitudes of all measured moduli were lower than in earlier studies (Fisher, 1969; Krag et al., 1997; Krag and Andreassen, 2003a). Ziebarth et al. (2011) used a conical probe to indent the lens capsule. These were highly localised measurements sensitive to any local variations in density or hydration and potentially to any changes to tissue structure that may have arisen during storage conditions of 4 °C for several days *post-mortem*. This varies from methods that have produced results applicable to the whole anterior or posterior sections (Fisher, 1969; Krag et al., 1997; Krag and Andreassen, 2003a).

4.3. The zonule

Fisher (1986) combined the method of centrifugation with uniaxial stretching to estimate the stretching forces when lenses, aged from 15 to 45 years old, subjected to the two tests demonstrated the same amount of thickness change (Fisher, 1977). Young's modulus was found to be 350 kPa and did not vary with age (Fisher, 1986). Van Alphen and Graebel (1991) measured the stretching force directly by treating the lens, zonular fibres and ciliary body as a single unit and fitting samples between two clamps to provide tension in two opposing directions. Young's moduli, at 10% strain were 1.0 MPa for young lenses aged 16 years and 1.5 MPa for older lenses with a mean age of 52 years. Michael et al. (2012) applied radial stretching to samples, which included the sclera and ciliary body as well as the lens and the zonular fibres, aged between 47 and 97 years. The samples were segmented into eight parts and connected to eight equally spaced hooks to avoid circumferential tension. The recorded force and elongation of zonular fibres demonstrated linear relationships within 10% strain. Young's modulus was found to be 340 kPa in samples aged between 47 and 60 years and 270 kPa in older lenses aged between 83 and 97 years. These are comparable magnitudes to those obtained by Fisher (1986).

4.4. Biomechanical implications for implants

Intraocular implant surgery is a routine part of cataract surgery and implant lens designs continue to be improved to enhance image quality and to prevent post-surgical complications, most notably secondary cataract from cellular adhesions on implant surfaces (reviewed in Saika, 2004). Many attempts at producing an accommodative implant that can simultaneously restore transparency as well as provide focussing power over the range of distances found in a young eye have been attempted (Wolffsohn and Davies, 2018; Alio et al., 2017; Sheppard et al., 2010). Current accommodative implants can be classified into three sub-groups: those that alter power by (a) axial movement of the whole or part of the implant; (b) shape alteration of the main optical component in response to the ciliary muscle contraction or (c) using multifocal optics to provide a wider range of clear focussing distances (Alio et al., 2017). The amount of accommodation that can be restored by these implants is limited or not yet reported (Alio et al., 2017). Biocompatible materials used for implant lenses: silicone, hydrophilic and hydrophobic acrylics, poly(methylacrylate) (PMMA) (Alio et al., 2017; Saika, 2004) have far higher Young's moduli and are, therefore, considerably stiffer than the natural lens. The determinants of biocompatibility are reviewed in Saika (2004).

If an implant is to truly mimic the action of the biological lens it should alter its shape in response to focussing demand. This has been

attempted using injectable polymers. Various materials have been considered (Hao et al., 2012; Parel et al., 1986; Yoo et al., 2007). Whilst the substances used are biocompatible (and those for which Young's modulus has been reported have magnitudes that are comparable to that of the human lens), there is a notable deterioration in transparency by six months after surgery in animal eyes (Hao et al., 2012; Kwon et al., 2005; Lee et al., 2014). None of these materials have been tested on *in vivo* human eyes.

4.5. Summary

With age stiffness across the lens increases and elastic modulus in the central regions, which is lower than the peripheral modulus in younger years, rises at a faster rate than the latter. The age at which the elastic modulus in lens centre may become greater than in the periphery cannot be concluded. Longitudinal and bulk moduli in the lens centre were found to be consistently higher than in the periphery at all measured ages and the width of the central region, rather than its magnitude, was found to increase with age. Whether loss of accommodation is attributed to increasing stiffness of the lens, growth in size of less pliable regions or a combination of both is a subject for further investigation.

5. Computational models

5.1. Analytical approaches

Modelling of lens biomechanics offers a necessary complement to experimental methods, making it possible to expand these beyond current limitations and to explore ranges of test parameters that experimentation does not allow. Both analytical and computational models have been used to investigate lens biomechanics. Early models (O'Neill and Doyle, 1968) employing analytical calculations treated the lens capsule as a thin shell with variations in capsular thickness (Fincham, 1937). The stress and displacement values of the thin shell model under zonular traction were numerically calculated by fitting to experimental data (von Helmholtz, 1866). O'Neill and Doyle (1968), pioneered the use of mechanical models to investigate deformability of the eye lens and demonstrated the critical importance of modelling parameters: the deformation of their model was dependent on capsular thickness. This analytical approach was also implemented in two subsequent studies (Chien et al., 2006; Reilly, 2014) that considered the volume of the lens within a capsular model assuming no change with zonular stretching. The resultant alterations in curvatures and optical powers were related to two accommodative theories (Helmholtz (1855); Schachar, 1994).

5.2. Finite Element analysis

Finite Element (FE) analysis has been used to develop models of the lens and the accommodative system. The method has wide-ranging applications beyond the biological and, with the advent of high-performance computing, models that simulate real world physical problems are now an integral part of design, prediction and analysis (Moaveni, 2007). Structures with complex geometries, a wide range of loadings and inhomogeneous and anisotropic material properties that often involve nonlinearities, are not easily solved by analytical mathematical methods.

Three general types of equations are contained in FE analysis, notably those that describe the geometrical continuity, those that describe the mechanical behaviour of the material of which the structure is composed and those that describe the force equilibria. The modelling approach segments the structure into a large number of components or elements of regular shape. These shapes are triangles or rectangles for two-dimensional problems and tetrahedrons or hexahedrons for three-dimensional problems. Elements are connected via nodes so that

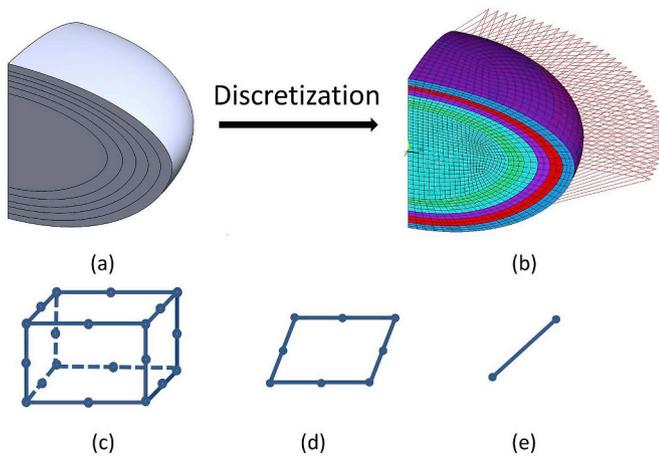


Fig. 12. The 35-year-old lens model used in Wang et al. (2016) showing: (a) lens geometry, (b) FE lens model discretized using elements for (c) the lens nucleus and cortex, (d) the lens capsule and (e) the zonule.

adjacent elements share nodes at a common boundary. An example of element types used in discretizing (creating a given model of discrete elements) is shown in Fig. 12. The three types of equations (describing geometry, material behaviour and forces) for each element and node are formulated and all equations combined to form a stiffness matrix, which is solved by computational analysis to provide solutions for the entire structure (Logan, 2011). Solutions can include an elucidation of geometrical changes, material behaviour and/or complex tissue interactions.

5.3. Modelling the human lens

The validity and precision of computational models are dependent on the accuracy of input parameters: geometrical shapes and material properties. Complete descriptions of intact lens shapes were not readily available in earlier studies resulting in geometries of lens models being assembled using parameters from several studies that had used different approaches (Burd et al., 2002). Knowledge of the exact locations of zonular attachments to the lens capsule as well as the directions and degrees of force applied to the lens via the zonule is scant. Coupled with the wide range of measurement techniques and consequent variations in lens biomechanical properties (as described in sections 3 and 4), construction of physiologically accurate models has not been without uncertainty and some degree of ambiguity. This notwithstanding, as the body of literature on material properties of the lens continues to grow and to include *in vivo* measurements, a more biologically factual picture is emerging. More recent models have striven to apply realistic shape parameters and model the dynamics of accommodation: changes in central surface curvatures, thickness and central optical powers so that these compare with changes seen *in vivo* (Wang et al., 2016, 2017).

5.4. Models of accommodation

Modelling the dynamics of accommodation has, just as have experimental methods of measuring biomechanics of the lens, produced varying results that have been difficult to reconcile. Conflicting theories of accommodation have remained divergent with models, in support of different theories, created (Coleman, 1970; Helmholtz, 1855; Schachar, 1992, 1994). The necessity of considering models using nonlinear formulation was originally emphasised by Burd et al. (1999) who demonstrated the difference in geometrical behaviour of lens models using linear and nonlinear formulations. This early FE modelling approach adopted a simple configuration containing only the lens capsule. Using nonlinear formulations, the models of Burd et al. (1999) showed that the central optical power decreases with increasing equatorial

strain, concurring with the classical theory of Helmholtz, 1855. Models constructed using linear formulations (Schachar et al., 1993) supported the accommodative theory of Schachar (1992). A subsequent study by Schachar and Bax (2001) using nonlinear FE models based on geometries of lenses aged 19 and 29 years (Brown, 1973) was used to test both theories of accommodation. Simulated stretching from anterior, posterior and equatorial zonular sections as well as from the anterior and posterior zonular sections only was applied to fully accommodated lenses to test the theory of Helmholtz; simulated stretching by the equatorial zonule only was applied to fully unaccommodated models to test the theory of Schachar (Schachar and Bax, 2001). The models used to test the theory of Schachar provided requisite support; those to test the theory of Helmholtz indicated that the force of stretching required to support the theory would be beyond what is physiological possible (Schachar and Bax, 2001). Models were based on the assumptions made by each theory about which set of zonular fibres provide the necessary force in the accommodative process (Schachar and Bax, 2001) and therefore could not provide an independent verification of either theory.

Burd et al. (2002) constructed three axisymmetric FE models based on previously reported geometric parameters from subjects aged 11, 29 and 45 years (Brown, 1973; Farnsworth and Shyne, 1979; Fincham, 1937; Fisher and Pettet, 1972; Strenk et al., 1999) and material properties (Fisher, 1969, 1971; Krag et al., 1996, 1997). An example of an axisymmetric model is shown in Fig. 13. The modelled lens surfaces near the paraxial regions became less curved with simulated stretching, in support of the theory of Helmholtz, 1855. The models used in this study did not adhere to physiological norms: the nucleus was defined by two circular arcs connected by a sharp point at both ends and the zonule was modelled as line segments attached to the capsule at three single points that resulted in sharp discontinuities in curvature with simulated stretching (Burd et al., 2002).

Martin et al. (2005) and Ljubimova et al. (2008), adopting models developed by Burd et al. (2002), incorporated the vitreous, to test the hypothesis of a role for the vitreous in accommodation that had been proposed by Coleman (1970). Martin et al. (2005) applied radial displacements (using values from Strenk et al., 1999) to lens models created to test the accommodative theory of Helmholtz, 1855 and an additional static pressure to the posterior lens surface to models used to test the accommodative theory of Coleman (1970). Martin et al. (2005), whose models included the capsule as a linear shell that did not have the malleable properties of the biological capsule, did not find any support for a vitreal role in accommodation. Ljubimova et al. (2008) tested two models with and without a vitreous; the vitreous was modelled as an incompressible body within a membrane of the same elasticity as the lens capsule. The findings of Ljubimova et al. (2008) supported the theory of Helmholtz (1855) but suggested an influence of the vitreous on accommodation with the acknowledgement of inaccuracies introduced in treating the vitreous as an elastic body.

Belaidi and Pierscionek (2007) emphasised that lens models should take account of changes in shape and material properties with age and created three dimensional models based on *in vitro* lenses that had undergone shape changes with stretching (Pierscionek, 1993). Models were created from 27 to 46 year old lenses and in both cases the nucleus was assumed to be two-thirds of the lens (Belaidi and Pierscionek, 2007). Models were created with a single elastic modulus and different elastic moduli for the nucleus and cortex, using values from Fisher (1971) and two levels of stretching force were simulated. A flattening of the peripheral lens curvatures with stretching was seen in all models. The central lens curvatures, however, showed both steepening and flattening depending on different lens geometries, distributions of material properties and amount of applied force. Both accommodative theories (Helmholtz, 1855; Schachar, 1994) were supported and depended on input parameters.

Wilkes and Reilly (2016) adopted a different approach to models that were subjected to simulated stretching by simulating an increase in

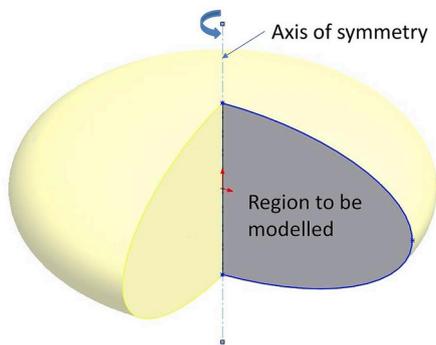


Fig. 13. Example of an axisymmetric model used in Finite Element Modelling.

curvature as in the process of accommodation. The models were based on two 20-year-old lens (Urs et al., 2009; Norrby, 2005) and used material properties from lenses aged between 14 and 62.7 years (Wilde et al., 2012). The increase in optical power for simulated accommodation was closest to clinical results (Anderson et al., 2008) for models based on younger ages. Models using material properties from presbyopic ages were still capable of simulating a change in optical power from which it was concluded that age-related changes in material parameters was not the sole cause for presbyopia (Wilkes and Reilly (2016).

5.5. Modelling the zonule and applied forces mediated by the zonule

The dynamic process of accommodation depends on forces imparted from the ciliary muscle via the zonule. This is the most difficult component of the accommodative apparatus to visualise during accommodation and, given its structural intricacies (Bron and Tripathi, 1998), the most complex component to model. Estimation of zonular forces involved in changing the lens shape has relied on modelling, however, without sufficient experimental knowledge models have been necessarily overly simplistic. Discontinuities in the equatorial region that were seen in earlier models (Burd et al., 2002; Martin et al., 2005) were avoided in later studies by excluding zonular fibres altogether from the FE model, instead applying uniformly distributed forces to the capsule around the equatorial zone (Hermans et al., 2006; Lanchares et al., 2012). Hermans et al. (2006) applied forces in three directions: in the equatorial plane and over a range of angles in the anterior and posterior directions and used an iterative process to minimise errors between the simulated stretched model and a reference lens in the fully unaccommodated form. Whilst this approach eliminated non-physiological discontinuities, it could only provide an estimate of the potential zonular force for a limited range of shape changes and without any relative distribution of forces in the different sections of the zonule. Two recent studies overcame the discontinuities created by introducing constraints to a number of neighbouring nodes surrounding each one of the three zonular anchorage points, thereby coupling the movements of these nodes to the corresponding zonular anchorage point (Wang et al., 2016, 2017).

Liu et al. (2006) developed a single lens model in which the zonule was created as three separate springs. The spring stiffness of the equatorial zonule was taken as one third of the stiffness of the anterior and posterior zonular springs. The springs were modelled as attached to the ciliary body at a single point and at three different points to simulate the underlying aspects of the Helmholtz, 1855 and Schachar (1992) theories respectively. Using the model with the single point of attachment to the ciliary body, the three zonular springs were stretched from this point of attachment in the equatorial direction; in the model with separate points of attachment to the ciliary body, the equatorial zonular spring moved in the opposite direction to its anterior and posterior counterparts (Liu et al., 2006). This study found support for

both accommodative theories, depending on what modelling configuration was applied. It should be noted that movement of springs towards the lens equator, as simulated in the model with three attachment points (Liu et al., 2006), would introduce a compression force that has no physiological basis.

A more complicated model of the zonular apparatus was created by Stachs et al. (2006) who proposed ten sets of zonular fibres and compared this model with the commonly simplified configuration using three sets of zonular fibres (Burd et al., 2002; Ljubimova et al., 2008; Martin et al., 2005). The findings showed that for equivalent amounts of applied radial displacement of the ciliary body there was negligible difference in the resultant central optical power whether a three set or ten set model of zonular fibres was used.

In the accommodation model of Wilkes and Reilly (2016), the zonule was created as a whole sector of meshed continuum elements, rather than as discrete elements seen in the majority of other models. Whether modelling the zonule as a whole or as composed of separate elements more closely mimics its behaviour during accommodation requires more comparative analysis between advanced models and *in vivo* findings.

The influence of zonular angles on optical performance of the lens was investigated more recently (Wang et al., 2016, 2017). Using a 35-year-old model and comparing results with *in vivo* measurements (Dubbelman et al., 2005), it was found that modelling the attachment of the equatorial, anterior and posterior zonular fibres to three separate stretching points can provide better physiological relevance than binding the three sets of zonular fibres to a single stretching point (Wang et al., 2016). An extensive and systematic parametric search of equatorial, anterior and posterior zonular angle combinations that were physiologically relevant, yielded 1815 possibilities and these were simulated for models based on 16 and 35 year old lenses (Wang et al., 2017). The resultant changes in radius of curvature with simulated stretching were compared to *in vivo* measurements of changes with accommodation (Dubbelman et al., 2005) and the results showed that anterior and posterior zonular angles exert the major influence on modelled lens shape change, with less effect from the equatorial zonular angle (Wang et al., 2017).

Hermans et al. (2008) considered potential age-related changes in zonular force to investigate the importance of material properties rather than to simulate and study zonular contributions to accommodation. Using material properties measured in three separate studies (Fisher, 1971; Heys et al., 2004; Weeber et al., 2007), Hermans et al. (2008) compared models undergoing simulated shape change with reference models of 11, 29 and 45 year old lenses constructed from a range of sources (Hermans et al., 2008). The averaged net force for stretching the lens into the unaccommodated state varied depending on the selection of material properties, none of which had been obtained from lenses in the physiological state. It is not possible to estimate which method could incur the greatest inaccuracies: centrifugation of whole lenses that does not replicate the stretch of the ciliary muscle or indentation of lenses, thawed from a frozen state and bisected and potentially at risk of some water loss and consequent change in material properties. Studies such as Hermans et al. (2008) illustrate the importance of choice of material parameters on the effects of simulated stretching and indicate a cautionary reliance on models given the potential inaccuracies of experimentally obtained parameters.

5.6. Opto-mechanical models

The inhomogeneous nature of the lens, which is manifested in a gradient of refractive index (Pierscionek and Regini, 2012), will have implications for biomechanics of the lens and relevance for models if these are to be as close as possible to the biological lens. The studies on BLS (Bailey et al., 2010; Besner et al., 2016) have confirmed that the bulk modulus follows a profile across the lens that is almost identical to that of the refractive index (Pierscionek et al., 2015). This makes it

easier to develop models that could be used to investigate opto-mechanical responses of lenses, which are currently not possible to measure directly *in vivo*. Detailed procedures for developing opto-mechanical lens models using both mechanical (ANSYS) and optical software (ZEMAX) packages were described by Riehemann et al. (2011) and Pour et al. (2015).

Pour et al. (2015) divided the lens into six major refractive surfaces: the outer capsular surface, the capsular-cortical interface and cortico-nuclear interface for both anterior and posterior segments and modelled changes in surface profiles for the unstretched state and for ten increments of stretch. The modelled surface profiles were subjected to optical ray tracing to calculate optical powers produced by the lens models (Pour et al., 2015). A mathematical function was developed that related the capsular, cortical and nuclear profiles (curvatures) to the amount of simulated stretching (Pour et al., 2015). Riehemann et al. (2011) described an opto-mechanical model of the eye using clinically obtained geometric and biometric data but with a simplification of the material properties and ignoring a slew of literature on the gradient refractive index (GRIN) of the lens. The claim that this model can be used to evaluate laser based treatment for presbyopia and other eye diseases (Riehemann et al., 2011) was not justified. Bahrami et al. (2016) used FE models to investigate redistribution of internal lens structures and consequent changes in the GRIN and Young's moduli profiles during accommodation. The modelled profiles were found to alter with accommodation by extension of the central section of the lens (Bahrami et al., 2016). This supports earlier clinical findings that showed a widening of the nucleus with accommodation (Brown, 1973; Dubbelman et al., 2003; Koretz et al., 1997; Patnaik, 1967).

5.7. Modelling gradient material properties

Contributions of gradient material properties to the age-related loss of accommodative ability were investigated by Weeber and van der Heijde (2007) using three axisymmetric lens models based on lenses aged 20, 40 and 60 years using equatorial diameters from Strenk et al. (1999) and anterior and posterior surface curvatures from Dubbelman et al. (2005). The material properties were either modelled as uniform, using values from Fisher (1971) or Weeber et al. (2005), or as a gradient distribution using measurements from Weeber et al. (2007). Lens models with uniformly distributed elastic moduli showed linear decreases in accommodative amplitude with age whilst models with gradient distributed material properties showed an accelerated decrease after 40 years of age. This accelerated decrease in lens accommodative ability in the fifth decade concurs with clinical findings (Duane, 1922) suggesting that models with gradients of elastic moduli may be better predictors of functional loss. Such models may also provide a more accurate analysis of stresses and strains in the lens than do models with uniform elastic moduli. The gradient moduli models of lenses aged 20, 40 and 60 years were used by Weeber and van der Heijde (2008) to test for changes in nuclear and cortical dimensions during accommodation. Strains in the nuclear region were found to be related to accommodative capacity (Weeber and van der Heijde, 2008). A recent study produced lens models of different ages: 16, 35 and 48 years with geometries of both lens nucleus and external lens shape taken from *in vitro* measurements (Bahrami et al., 2014). Both uniform and gradient distributions of elastic moduli were modelled in the lens cortex for each age (Wang et al., 2016) based on material properties taken from two studies that applied a spinning method of measurement (Fisher, 1971; Wilde et al., 2012). The results show that with simulated stretching, gradient moduli lens models had lower stress concentrations at the cortico-nuclear boundaries than equivalent models with uniform elastic moduli. Stresses in the equatorial region of lenses near the cortico-nuclear boundaries became more evenly distributed as the number of cortical layers were increased and gradient of elastic moduli rendered more refined (Wang et al., 2016).

5.8. Verifying the effectiveness of surgical treatments

The use of FE models for prediction of surgical outcomes (Burd and Wilde, 2016; Pour et al., 2013; Ripken et al., 2006) has wide ranging, and as yet, relatively unexplored potential. Models have been used to investigate materials that could be applicable for restoring accommodative ability: a material of equivalent isotropic Young's modulus could restore a significant proportion of accommodation but the value of further exploring the effect of a gradient modulus on accommodation was acknowledged (Pour et al., 2013). Biomechanical modelling has been used to test different surgical incisions made by a femtosecond laser in an attempt to evaluate this as a treatment for presbyopia (Ripken et al., 2006). The change in deformability of porcine lenses, subjected to various types of laser cuts, was evaluated by applying centrifugal forces and compared to an FE model with human geometries using values of Young's modulus taken from Fisher (1971) and Krag et al. (1996) for the lens and the lens capsule respectively. The model predicted no clinically significant change in accommodative amplitude after femtosecond surgery: the reported 15.2% difference between 'treated' and 'untreated' was equivalent to 0.27 dioptres (Ripken et al., 2006). A great deal more investigation and experimentally relevant input data are needed before such a modelling approach can be deemed sufficiently robust to predict the outcomes of femtosecond laser surgery for treatment of presbyopia.

A recent study has used FE modelling to evaluate different arrangements of cutting planes in the lens along radial directions to determine the potential improvements of the accommodative performance of a lens subjected to lentotomy cuts (Burd and Wilde, 2016). The difference in predicted effectiveness of radial cuts, depending on whether the material of the lens was modelled as poroelastic (and therefore compressible) or as incompressible, was compared using a 45-year-old human lens model (Burd and Wilde, 2016). It reinforced the need to determine accurate constitutive models.

5.9. Summary

Models developed to simulate various aspects of lens biomechanics include those that examine the deformable behaviour of lenses during accommodation, those that investigate the sensitivity of models to a certain parameter that is used to construct the model, ie distributions of material properties and zonular angles, and those that predict the outcome of clinical surgeries. Models have been based on limited numbers of lenses and age ranges. Using models to test the theories of accommodation has limitations. The results are dependent on the structure of the models, the shapes of lenses, the material properties of the lens and the configuration and attachment of the zonular sections. It may also depend on whether or not a vitreous support is included. It would be more appropriate to create models that seek to mimic experimental measures of the *in vivo* accommodating lens and incrementally determine which parameters produce the most physiologically relevant models, bearing in mind that there may not be a unique set of parameters, but a plausible range.

The dependence of models on input parameters, some of which are not yet experimentally possible to obtain, mean that models need to be tested and optimised against clinical data. Simplifications, particular in modelling of the zonule, have to be taken into account as arrangements of zonular sections, and how these are attached to the capsule, has an effect on modelled results. As models are further refined, experimental data on biomechanical properties from *in vivo* lenses become available and computational resources advance, more sophisticated models will be constructed. Models need to take into account the lamellar nature of the lens and how this influences the optical and biomechanical properties to be truly representative of the biological lens and better predictors of its function. Modelling of surgical treatments requires far greater precision and levels of accuracy in the measurement of material properties than is currently possible, if reliance on models and their

predictive capability is to become an integral part of surgical procedure.

6. Biomechanical analysis of functional loss

6.1. Presbyopia

Factors thought to contribute to the development of presbyopia can be broadly divided into three categories: (i) age-related changes in biomechanical properties of the lens and capsule, (ii) growth and age-related alterations in lens shape and relative geometries of components involved in accommodation and (iii) age-related changes in biomechanical properties of the zonule and ciliary muscle.

Age-related changes in the lens material properties have been reported (Fisher, 1971; Heys et al., 2004; Weeber et al., 2007; Wilde et al., 2012) and the major causal factor that has been proposed for these changes is the continued accrual of lens cells with age resulting in compaction, rendering the lens less pliable (reviewed in Werner et al., 2000). The assumption that lens fibres undergo compaction with age may appear incompatible with that of an incompressible lens material. Yet, these explanations can be reconciled. Compaction, if indeed it occurs, is a gradual, long-term process that is a consequence of changes in conformations of proteins and in the protein-water relationship (Lahm et al., 1985); at any given time, however, the lens material may still be incompressible. Some studies have reported that lens volume may alter slightly with accommodation (Strenk et al., 2004; Gerometta et al., 2007; Sheppard et al., 2011) which would suggest that the lens may be to some degree compressible. These findings are inconclusive. Even when considering results from the most physiologically relevant studies conducted on *in vivo* lenses (Strenk et al., 2004; Sheppard et al., 2011), these have not been supported by findings from investigations using comparable methods (Hermans et al., 2009) or other techniques (Martinez-Enriquez et al., 2017).

The lens capsule was thought to become less able, with age, to mould an increasingly less malleable lens into the accommodated form (Fincham, 1937). (It should be noted that this proposal is in contradiction with the theory of Helmholtz (1855)). Some support for capsular changes with age that were postulated by Fincham (1937) was seen in results from experimental measurements of capsular elasticity conducted by Fisher (1969). Young's modulus of the anterior capsule was reported to decrease with age until well into the seventh decade (Fisher, 1969, as reviewed in section 4.2). This decrease in modulus was considered to be because the ageing capsule becomes more flaccid (Fisher, 1969). It was subsequently noted that Fisher's data was taken from the non-physiological part of stress-strain curves and that the elastic modulus of the lens capsule, especially the anterior portion, increases until the age at which presbyopia becomes manifest (Krag and Andreassen, 2003a). An increase in Young's modulus of the capsule with age was also found by Ziebarth et al. (2011). This apparent contradiction to the results of Fisher (1969) occurs because Ziebarth et al. (2011), calculated the modulus from the force of indentation which showed an increased resistance of the ageing capsule to the force. Fisher (1969) who used stretching, found that the more flaccid older capsule, yielded more easily than a younger lens to a stretching force. No age-related change in Young's modulus of the zonule was found (Michael et al., 2012); this has not been considered a factor in presbyopia.

Age-related changes in shape of the lens and in relative geometry of the accommodative system (Koretz and Handelman, 1988; Pierscionek and Weale, 1995) have support from a number of experimental sources. It is known that the continual growth of the lens throughout life results in an increase in cross-sectional area and in thickness of the lens. The ciliary muscle appears to move anteriorly and towards the lens anterior pole with age, suggesting that the ciliary body thickens (Pardue and Sivak, 2000; Sheppard and Davies, 2011; Tamm et al., 1992). The biomechanical significance of these changes in geometry are that an increase in equatorial dimension coupled with a decrease in the ciliary ring diameter would leave less space for zonular fibres to be stretched,

thereby decreasing zonular tension with age. Another change in geometrical aspects of the accommodative system with age was reported by Farnsworth and Shyne (1979) who were the first to show that the anterior zonular attachment positions appear to move to a more anterior position, an effect caused by the continual growth of the lens. This alters the relative angles of zonular force that can be applied to the lens and as the anterior zonule approaches a tangent to the lens surface (Koretz and Handelman, 1986, 1988), the ability of zonular forces to alter lens shape progressively diminish (Pierscionek and Weale, 1995).

The contractibility of the ciliary muscle was demonstrated to be retained long after the onset of presbyopia using impedance cyclography (Swegmark, 1969) and more recently using MRI (Sheppard and Davies, 2011). The relative contribution of any of these factors to the process of presbyopia is difficult to ascertain experimentally.

Schachar et al. (2006) determined the critical values of different parameters that contribute to accommodative loss using five axisymmetric lens models based on lens profiles fitted from published MRI images (Lizak et al., 2000; Strenk et al., 1999). Models of a 20-year-old and a 40-year-old lens in accommodated and unaccommodated states and of a 60-year-old lens in an unaccommodated state were created. The modelling took into account the thickness and biomechanical properties of the lens capsule, the strength of attachment between the lens capsule and the lens substance, biomechanical properties of the zonular fibres and elastic moduli of the lens nucleus and cortex. The decrease in central optical power with simulated stretching was found to be related solely to an increase in the elastic modulus of the lens model (Schachar et al., 2006). This is in contradiction to the conclusions of Wilkes and Reilly (2016) (described in section 5.4).

Abolmaali et al. (2007) extended the models of Schachar et al. (2006) adding three types of zonular traction: by equatorial zonular fibre alone, by the anterior and posterior zonular fibres acting together or by all three sections of the zonule. For all types of zonular traction, the stretching point emanated from same point, forces applied along the equatorial direction and variations in anchorage points of the anterior and posterior zonule on the capsule were tested. The closer the proximity of zonular attachment to the lens equator, the greater the change in central optical power supporting the reduction of distance between the ciliary body and the lens as a causal factor in presbyopia (Abolmaali et al., 2007).

Van de Sompel et al. (2010) investigated the roles of lens shape and material properties on the development of presbyopia based on two lens models aged 29 and 45 years from Burd et al. (2002) and taking into account the lens GRIN profile in the calculation of optical power. A range of lens shapes and material properties and various combinations were modelled and the simulations suggested that changes in lens geometry were the predominant causal factor in presbyopia.

6.2. Cataract

Diminution of transparency is accepted as the functional consequence of cataract; biomechanical changes are relatively rarely considered. The most common form of cataract, senile cataract, generally affects sight after the age at which accommodative capacity is lost. The pathological processes that lead to cataract, have been found to have an effect on biomechanics of the lens. Older lenses were found to have a stiffer lens nucleus (Fisher, 1971; Heys et al., 2004) and, given that ageing is a risk factor for senile cataract, the concomitant increase in resistance to stretching forces that are imposed on the lens to alter its shape may create local stresses in presbyopic lenses that cause damage to lens fibre and result in spoke-shaped opacities (Fisher, 1973). It was noted by Michael and Bron (2011) that the age at which radial and circular opacities are seen in the equatorial region of the lens corresponds with the age at which the shear modulus of the nucleus increases above that of the cortex (Heys et al., 2004). Local opacities have been postulated to arise because of regional stresses in the lens cortex induced by applied forces of the ciliary muscle (Brown et al., 1993; Pau,

2006; Michael and Bron, 2011; Michael et al., 2008) or because of compaction of cortical fibres against the nucleus (Harding et al., 1985). The latter suggestion has support from *in vivo* and *in vitro* findings. The majority of deformation that occurs during accommodation is seen in the lens nucleus (Brown, 1973; Dubbelman et al., 2003; Koretz et al., 1997; Patnaik, 1967; Strenk et al., 1999). Given that the nucleus loses this capacity with age, stresses could be caused by cortical fibres being 'pressed' or compacted against an increasingly stiffer nucleus (Harding et al., 1985). Observations from *in vitro* studies have reported small opacities around the cortico-nuclear boundary (Michael et al., 2008; Obazawa et al., 1983; Vrensen and Willekens, 1990). Computational modelling studies, using lens models with different moduli for cortex and nucleus, have indeed demonstrated a high stress concentration region near the cortico-nuclear equator (Belaidi and Pierscionek, 2007; Wang et al., 2016). Future mechanical analysis, combining both experimental and computational methods, are needed to further investigate the potential that such stresses can lead to the formation of cortical cataract. Recent findings, that have shown circulation of ions and fluid in the lens to be critical to maintaining the refractive index gradient (Donaldson et al., 2017; Vaghefi et al., 2015), have relevance to changes in mechanical properties when these circulating systems are disrupted. This warrants further investigation.

Patel et al. (2013), using AFM, compared Young's moduli of anterior lens capsules removed during cataract extraction surgery. A greater capsular stiffness, compared to capsules from healthy controls, was noted only in capsules from lenses with nuclear cataract (Patel et al., 2013). Choi et al. (2012) reported a somewhat different finding using the same method as Patel et al. (2013), notably that capsular Young's moduli from cataractous lenses were higher than those from a control group. The cataract types were, however, not given. Significantly higher values of Young's moduli of anterior capsules from cataractous lenses compared to literature values of capsules from healthy human lenses (Fisher, 1969; Krag and Andreassen, 2003b; Ziebarth et al., 2011) were reported by Simsek et al. (2017). It is notable that diabetes, which can exacerbate cataractogenesis, may also have an effect on capsular biomechanics. Lens capsules from diabetics were more vulnerable to rupture during extraction surgery (Ramsell, 1969) and were found to be less pliable than capsules from clear lenses (Pedrigi et al., 2007).

6.3. Summary

With age, the lens loses optical and biomechanical function. The former has been linked traditionally with cataract; the latter with presbyopia. Both optical and mechanical properties are dependent on the structural entities, the proteins and water in the lens, and hence age-related changes in structure will manifest on both refraction and biomechanics. The similarities between gradients of refractive index and gradients of moduli suggest that the relationship between these two parameters may be linear. Though ageing occurs at different rates and some trends with age may be masked by individual variations, probing the opto-mechanical relationship is needed for a better understanding of presbyopia and cataract.

7. Conclusion and reflections

Biomechanics and its relationship to structural features, notably the crystallin proteins, has been less prominent than optics in studies on, theories of and conclusions reached about the structure/function relationship of the lens. Given that the fundamental action in the accommodative process which leads to an optical adjustment, that of focussing, is a mechanical change in shape and that theories and hypotheses have indirectly alluded to this, it may appear unusual that greater emphasis has not been given to the biomechanical parameters. The reasons for this can, at least in part, be attributed to the difficulties in measuring biomechanics of this biological system and particularly *in*

vivo when the action of accommodation is occurring. There are also inconsistencies in the biomechanical parameter that is measured as different techniques provide different measures, some of which are inconvertible preventing direct comparisons from being made between certain studies.

7.1. Unanswered questions

Measurements of the various moduli require conversions if any comparisons are to be made. Even though these conversions may be possible mathematically, the absence of knowledge about Poisson's ratio renders any such conversion an approximation. This is particularly sensitive when Poisson's ratio appears in the denominator and very small increments in this parameter yield very large differences in the calculated modulus. Before developing techniques to accurately measure Poisson's ratio of the various component tissues involved in accommodation, a valid constitutive model is needed to describe the fibre cell structure, interaction between cell membranes and cytosolic components.

Whilst the loss of transparency is considered to be caused by biochemical alterations in crystallin proteins and the relationship between crystallin sub-classes and water, mechanically induced strains that can rupture cells have been causally linked to localised opacities. This poses an interesting dilemma. For if indeed, the force of stretching causes opacities to develop in older lenses, it could only be from tension of the zonule as it maintains the lens in the unaccommodated state or from the attempts of an older lens to accommodate. If it is the former, why are these opacities not seen in younger lenses? If it is the latter, which would be consistent with such opacities being found only in older lenses, it contradicts the well-established theory of Helmholtz for this theory holds that accommodation is caused by relaxation of the zonule. Future investigations should maintain an open-minded approach when interpreting results and observations, mindful of the fact that there remains a paucity of understanding of the zonular forces on the lens and, until that is resolved, either of the current theories, may have credence. Indeed, alterations in biomechanics and geometrical features of the accommodative system with age may indicate support for aspects of more than one theory.

7.2. Future directions

Variations in the biomechanical parameter that is measured should not be considered a hindrance or limitation but rather as forming a wider spectrum of information, provided that these variations are biological and not experimentally induced artefacts. Such information can collectively provide necessary insights about age-related trends, how parameters may vary under measurement conditions and the magnitude and directions of forces that are compatible with those generated by the ciliary and mediated by the zonule. A greater compatibility of input parameters: material properties and forces, will allow further and much needed refinement of models of the lens and accommodative system. This will lead to the design of reliable models that can be used to predict lens shape change and identify, with high degrees of accuracy, where stresses and strains occur when a lens of any given age within an eyeball of any given biometry is subjected to stretching forces. The prediction of stresses and strains has relevance for understanding the development of cataract.

Far greater understanding of the biomechanical properties of the lens and accommodative system, how they alter with age and how they may vary with refractive error and individual ocular biometry is needed for creation of physiologically relevant models of implant lenses that can mimic the accommodative system of the eye. This requires a great deal of innovative research into how capsular biomechanics may alter after capsulorhexis and the effect that this may have on mechanical behaviour of the accommodative system. It also paves the way to developing designs that prompt newer surgical techniques with a different

type of incision that minimises capsular loss. Ultimately, future investigations should aim to probe more closely the relationship between mechanics, optics and biochemistry of the lens and accommodative components for a complete understanding of the structure/function relationship of this optomechanical system.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.preteyeres.2018.11.004>.

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