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Modelling the human retina in patients with glaucoma

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Abstract: Glaucoma is a major risk factor for blindness and causes loss of visual field due to retinal ganglion cell (RGC) destruction. Glaucoma is associated with high blood pressure, cardiovascular disease, and ocular blood flow. Vascular factors play an important role in the development of glaucoma. A number of retinal vascular parameters are measured for use in software from retinal imaging. The biomechanical model of the disease reveals that mechanical stress induced by IOP impairs the function of retinal ganglion cells. Due to the difficulty of direct retinal biomechanical measurement in determining ocular biomechanics, the current study uses modeling with significant limitations to make it easier to examine.The purpose of this article is to stimulate the human retina in patients with glaucoma. In this research, the applied stresses on the inner surfaces of the retina and its effects on the inner parts are studied. Intraocular pressure (IOP) is considered to be higher than 20 mm Hg. With this model, we can study stresses and strains in different and desired conditions. The way of applying load is compressive load on the retina.

Keywords: Glaucoma, Intraocular pressure, Retina, Finite element method, Stress, Strain

1. Introduction

Glaucoma encompasses a group of eye conditions, which cause progressive optic nerve damage, retinal ganglion cell death, and corresponding visual field defects. It is the third leading cause of global blindness after uncorrected refractive error and cataract.[1] More importantly with ageing, time with glaucoma diagnosis will be longer and the lifetime risk of blindness will increase correspondingly[2] The most common type of glaucoma is primary open-angle glaucoma (POAG) with normal, open anterior chamber angle and restricted aqueous outflow associated with increased intraocular pressure (IOP), i.e. high-pressure glaucoma. There is no evidence of a threshold IOP for the onset of glaucoma, but the relative risk for the disease rises with the level of IOP. Nevertheless, most subjects with IOP outside the “normal” range (ocular hypertension) in a population will not develop POAG [3] Though these IOP-lowering therapies have been proven to slow and/or halt progression of the glaucomatous damage and therefore are neuroprotective in nature, slow progress has been made in developing IOP-independent neuroprotection and/or neuroregeneration strategies[4]

In addition, early stage intervention to prevent disease development and/or progression would likely require evolution of improved algorithms and technologies to enable and/or enhance this earlier detection. Novel experimental strategies are exploring disease modification/intervention to prevent against optic nerve head (ONH) damage and/or retinal ganglion cell (RGC) death without depending on IOP lowering. One upstream goal would target intervention at an early stage of the glaucomatous disease process to halt or slow down the

underlying neurodegenerative process. Various etiologies for RGC death have been implicated including defective axonal transport, ischemia, excitotoxicity, reactive oxygen species, trophic factor withdrawal, and loss of RGC electrical activity[5]

2. Mechanisms of RGC

Loss of RGCs has been identified as the earliest form of cell death in glaucoma, and reduction in RGC function is ultimately considered responsible for visual field loss [6]. The human retina contains approximately 1.5 million RGCs [7] with an estimated rate of RGC loss of 0.4 % per year due to normal physiological ageing, increasing to 4 % per year in glaucoma patients [8]. RGC death in glaucoma is thought to predominantly occur through apoptosis, although other forms of cell death do occur[9]. Due to the complex and multifactorial nature of glaucoma (Table 1), multiple mechanisms are thought to contribute to RGC loss. Observations that axotomy precedes RGC soma loss by a period of several days in rodent models of axotomy and IOP elevation using the retrograde label Fluorogold have long hinted that changes at the level of the RGC axon precede apoptotic degeneration of the RGC soma [10]. More recent support for this view was presented by Calkins, who in summarising the results of several rodent studies using the acute IOP Morrison's model of ocular hypertension found that axonal degeneration typically occurs at a 2–3-fold greater extent than RGC soma loss and exhibits a stronger positive correlation with IOP exposure [11].

The diagnosis of glaucoma is presently achieved using a combination of both functional and structural assessments. The standard automated perimetry is primarily used to assess functional deficits in glaucoma patients, while structural diagnostic tools are principally based on the quantification of retinal nerve fibre layer (RNFL) thickness changes by optical coherence tomography (OCT) and disc tomography (confocal laser-scanning tomography) to assess structural changes at the site of the optic nerve head (ONH). Clinical assessment of the optic disc using slit lamp examination is not surpassed by recent advances in structural imaging techniques. Slit lamp biomicroscopy is required to assess the colour or pallor of the disc, disc haemorrhages, and factors associated with secondary glaucomas, such as neovascularisation of the disc, retina, iris and drainage angle, uveitis, pseudoexfoliation, pigment dispersion, primary or secondary iris transillumination, trauma, and gonioscopic assessment of the drainage angle.[12]

Table 1 : Overview of identified risk factors for POAG

Parameter	Trend
IOP elevation	Increased incidence and prevalence. Increased rate of progression (RoP); elevated IOP compared to normal IOP—Canadian glaucoma study odds ratio (OR) 1.19, European glaucoma prevention study OR 1.12
Age	Increased incidence and prevalence; Hispanics and people of European ancestry showed a steeper increase in POAG prevalence with age compared with African and Asian populations
Race	Increased incidence and prevalence of POAG in African (highest prevalence worldwide, 4.2 %

	of African population), Afro-Caribbean and coloured American population
Inheritance	Increased incidence and prevalence First degree relative with glaucoma increases POAG risk ten-fold POAG exhibits minor but significant heritability (twin study)
Myopia	Increased RoP, OR of 1.65 between low myopia (myopia up to -3D) and glaucoma and OR of 2.46 between high myopia (≤-3D myopic) and glaucoma
Cornea thickness	Increased incidence and prevalence in patients presenting with a thin cornea thickness, African American participants had a thinner central corneal measurement (554.9 ± 38.5 µm) than other participants (578.3 ± 36.5 µm)
Blood pressure abnormality	Increased incidence and prevalence with low systolic pressure, increased severity with diurnal pressure fluctuations and lower diastolic blood pressure, especially during night time

Stress to RGCs in glaucoma progresses in both directions from the nerve head: retrograde towards the RGC body in the retina and anterograde towards central axonal targets in the brain[13].In the retrograde direction, RGC dendritic arbors experience pruning, with loss of excitatory synapses. In the anterograde direction, active axonal transport from the retina to central brain terminals diminishes early in progression, with subsequent disassembly of the myelinated axon in the nerve and degradation of post-synaptic targets in the brain [14]. Importantly, the unmyelinated axon segment in the retina and proximal nerve head remains intact along with the RGC body long after degeneration of the rest of the axon and pruning of the dendritic arbor. The optic nerve head is therefore a critical locus in the degeneration of RGCs and understanding the underlying mechanisms is key to developing protective, reparative, and regenerative strategies to preserve the optic projection and prevent vision loss in glaucoma.

Ideally, neuroprotective strategies should prevent RGC dysfunction and thus subsequent degeneration while promoting repair or even regeneration of damaged tissue to restore vision, as reviewed elsewhere [15]. While clinical neuroprotective trials have proven difficult [16] therapies involving growth factors may have the potential to achieve those goals.

RGC dendrites are dynamic during development, expanding and contracting in response to environmental stimuli, but become stable when cells reach maturity [17]. Shrinkage of dendritic arbors occurs before complete degeneration of cells; thus, dendritic regeneration is a crucial step in the replenishment of RGC health and function [18]

3. Materials and Methods:

This study, investigates the applied stresses on the inner surface of the retina and its effects on the inner parts. Due to the symmetry of the components, the analysis is performed symmetrically. The properties defined in this project are listed on the table1. A compressive load of 5 KPa is placed on the retina to obtain the results and the amount of stress applied. An anatomical schematic of the eye with its components is shown below, which we use for designing and modeling in *Abaqus* software:

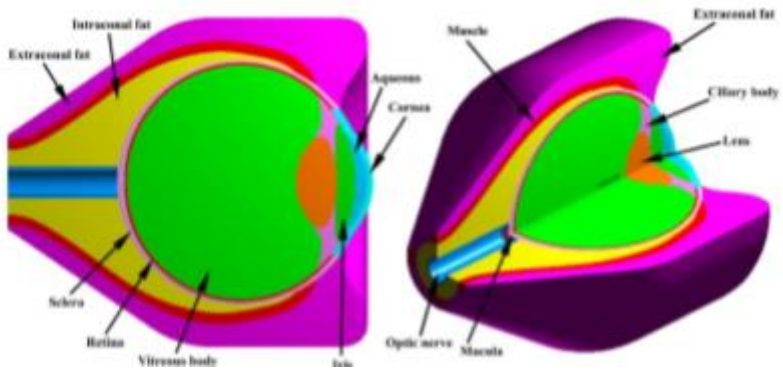


Fig1: Eye schematic

According to the following table, we consider the mechanical properties of the specified parts of the human eye in the software:

Table2: The element type, material model, density and material parameters of the human eye FE model

Eye component	**Element type**	**Material model**	**Density**	**Material parameters (Reference)**
Cornea	Lagrangian	Elastic	**1143**	E=1.5 MPa
Aqueous	ALE	Shock EOS	**1000**	μ(viscosity)= 7.5 *10 Pas, C=1530 m/s, s=2.1057
Ciliary body	Lagrangian	Hyperelastic	**1000**	μ =43.05 kPa, 2-37.7 kPa, a=54.255, a2=48.072
Lens	Lagrangian	Elastic	**1600**	E=6.88 MPa
Vitreous	Lagrangian	Elastic	**1078**	Go=10PA, G=0.3 Pa, B=14.3 s, K=2000 MPa
Retina	Lagrangian	Viscoelastic	**950**	E=20 kPa
Sclera	Lagrangian	Elastic	**1110**	E=5.5 MPa, v=D0.47

Optic nerve	Lagrangian	Elastic	**1243**	E=5.5 MPa, v=0.47
Muscle	Lagrangian	Elastic	**1060**	E=40 kPa

After determining the coefficient of elasticity, Poisson's coefficient and mechanical properties and compressive loading on the surface of the retina, the maximum amount of stress is specified in the following figure:

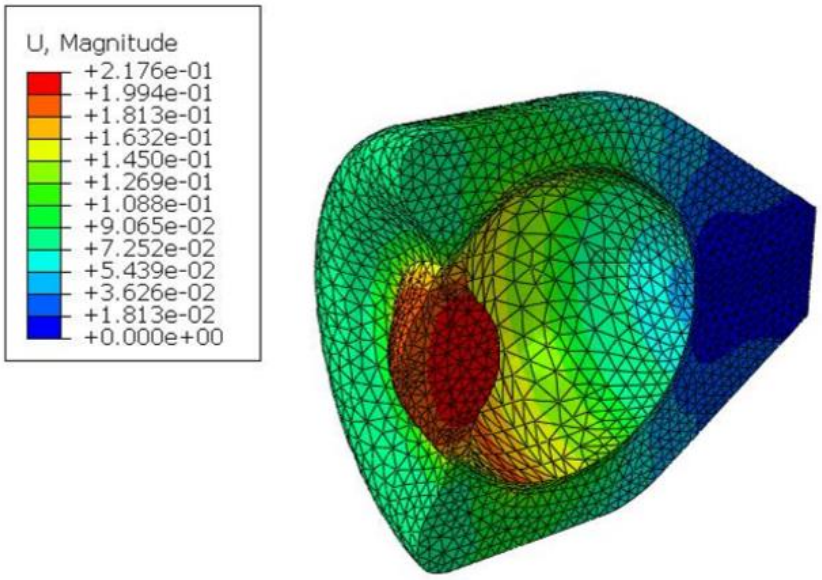
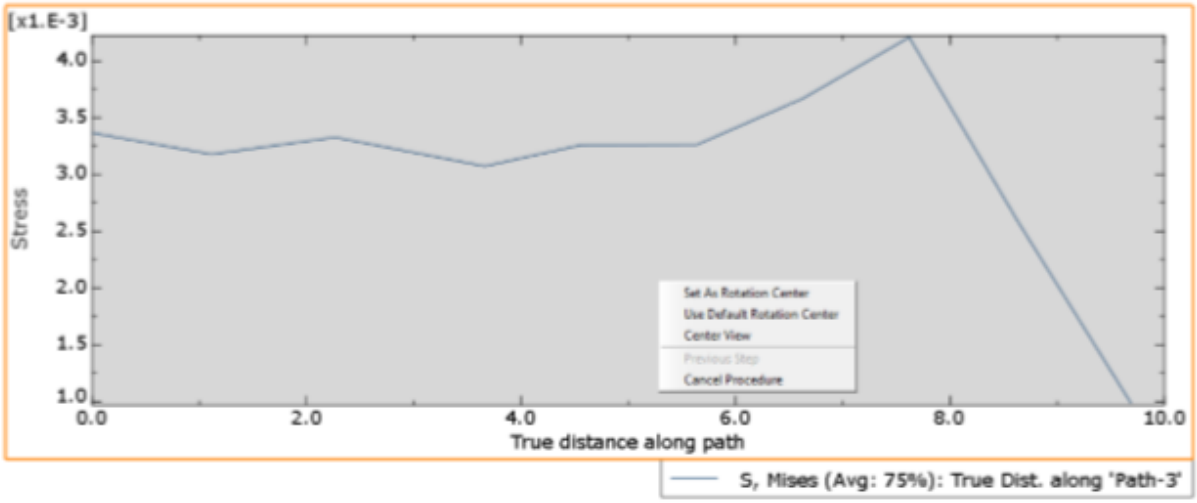


Fig2: Displacement contour for eye



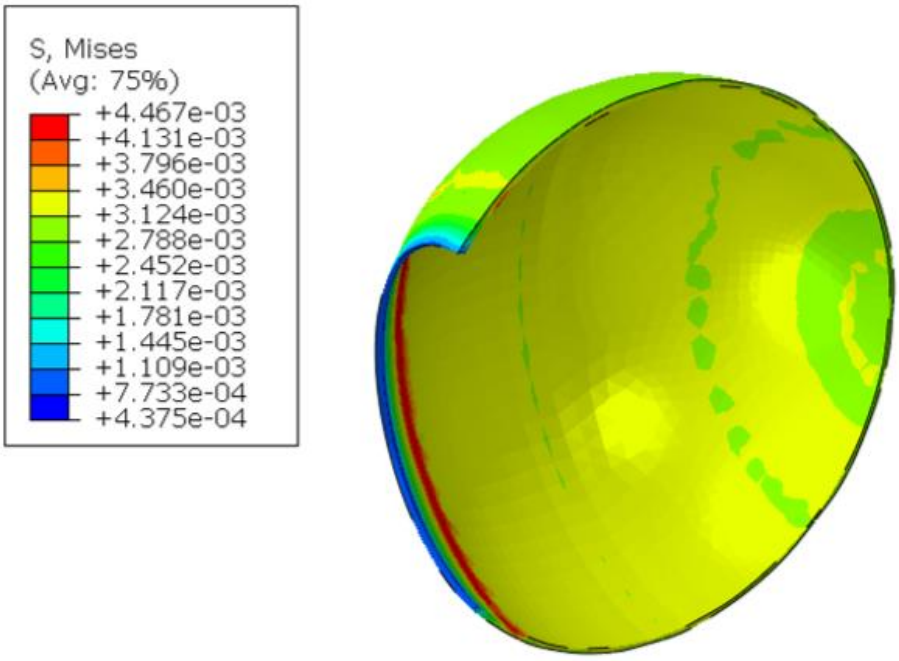


Fig3: Stress created on the retina

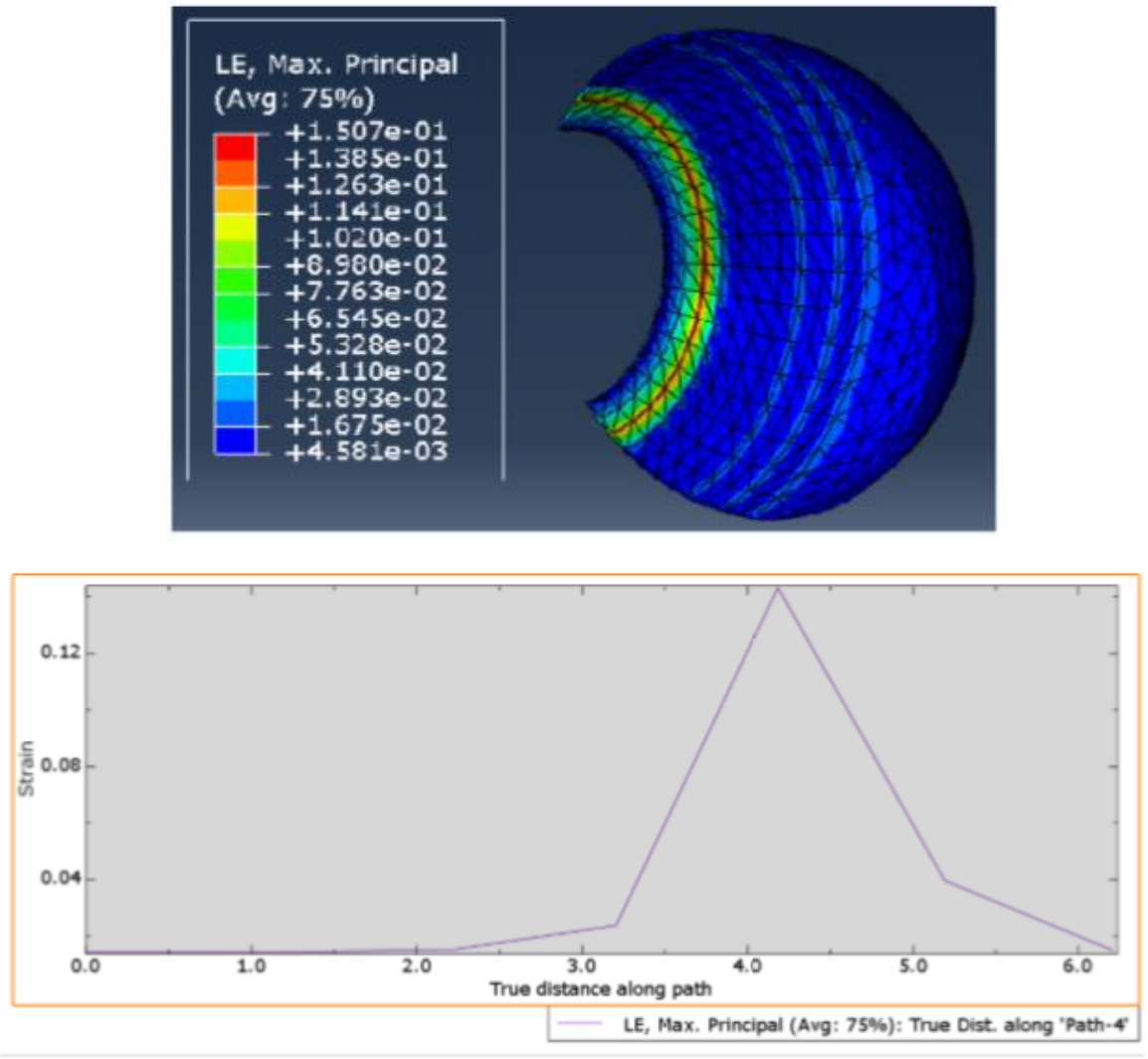


Fig4: Strain created on the retina

4. Results and Discussion:

In people with glaucoma, the amount of retinal stress obtained from the simulation results is about 67.44 KPa in the area and the pressure load in the software is 5 KPa.

To evaluate the calculated stress, the eye is considered as a sphere under pressure. For stress in the sphere, the stress-pressure relationship is used. The amount of tension in the retina is directly related to the increase of intraocular pressure and the decrease of thickness. Increased intraocular pressure causes the death of retinal ganglion cells, which reduces the thickness of the retina, and this also causes retinal rupture in people with glaucoma.

We conclude that glaucoma is the cause of increased stress and pressure is only one of the determinants of stress. However, stress also depends on other factors such as thickness. Stress causes strain and blockage of retinal blood vessels. In fact, a set of factors together determine whether a person has glaucoma or not. These factors include thickness, inner radius of the eye, and resistance to stress. These three factors are different among people and therefore the risk of glaucoma is also different in people.

High IOP (IOP) puts stress on the retina, which leads to rupture or perforation of the retina and eventually blindness. This article was reviewed for people with glaucoma who had high eye pressure, but due to the complexity of this disease, the amount of damage in people with normal eye pressure and glaucoma can also be examined.

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