INTRODUCTION

Glaucoma is a leading cause of blindness in the world and is due to the loss of retinal ganglion cell axons. These axons deteriorate in a region in the posterior pole of the eye known as the optic nerve head (ONH). The axons pass through the lamina cribrosa (LC) as they exit the eye at the ONH. The LC is characterized by a porous, connective tissue structure composed of laminar beams. The function of the LC is unclear, but is believed to include providing mechanical support to the axons as they transition from inside the pressurized globe to the lower pressure orbital space.

Early experimental glaucoma studies have shown that the LC remodels into a thicker, more posterior structure which incorporates more connective tissue after chronic IOP elevation \[1,2\]. The process by which this occurs is unknown. These structural changes are assumed to play an important role in the pathophysiology of the ocular disease glaucoma, where elevated IOP is known to be the most relevant risk factor.

In this paper we present a microstructure motivated growth and remodeling (G&R) formulation to computationally simulate and explore a potential mechanism of these structural changes seen in earliest stages of glaucoma.

METHODS

Collagen fibrils are thought to be constantly removed and deposited in the LC. We hypothesize that an up- or down-regulated synthesis or degradation of collagen fibrils may alter the collagen content and cause the G&R response of the LC seen in early experimental glaucoma. LC thickening is thus assumed to be a consequence of collagen fibril mass increase.

Growth and Remodeling Stimulus

In accordance with \[3\], we hypothesize that the elastic stretch \( \lambda_{fib} \) experienced by the collagen fibril material will stimulate the G&R response of the LC. The proposed stimulus is based on the idea that G&R occurs in an effort to maintain a homeostatic elastic stretch environment \( \lambda_{hom} \) at the collagen fibril level \( \lambda_{fib} \rightarrow \lambda_{hom} \). We define the G&R stimulus function as

\[
\phi = \lambda_{fib} - \lambda_{hom},
\]

where the homeostatic state is represented by \( \phi = 0 \).

Collagen Fibril Crimp and Residual Strains

We assume that the elastic stretch of the collagen fibril material at the micro-scale differs from the elastic stretch of the tissue at the macro-scale due to collagen fibril crimping and development of residual strains. The macroscopic elastic stretch of the bulk tissue \( \lambda_e \) is thus multiplicatively decomposed into the residual stretch \( \lambda_R \), a part \( \lambda^{crimp} \) representing the geometrical (un-)crimping of the fibril, and the elastic stretch of the fibril material \( \lambda_{fib} \) based on \[4\]

\[
\lambda_e = \lambda_R \lambda^{crimp} \lambda_{fib}. \tag{2}
\]

Residual strain between the collagen fibrils and the surrounding matrix material is assumed to evolve due to the continuous collagen fibril turnover. Similar to \[5\], we propose a remodeling rule for the adaptation of the residual stretch \( \lambda_R \)

\[
\dot{\lambda}_R = \frac{1}{\tau_R} \phi, \tag{3}
\]

where the parameter \( \tau_R \) in \( \text{(3)} \) relates to the remodeling time needed to achieve homeostasis.

Collagen Fibril Synthesis and Degradation

We assume that the LC tissue volume includes three constituents: (i) the collagen fibrils; (ii) the axon bundles and (iii) the surrounding matrix material. Furthermore, the volume occupied by collagen fibrils

\footnote{Corresponding author, email: rafael@grytz.de}
can change due to changes in collagen fibril synthesis or degradation stimulated by (1). We introduce a simple evolution equation for the change in collagen fibril volume \( \frac{dV}{dt} = \frac{dV_{\text{col}}}{dt} \) from the initial to the grown configuration

\[
\frac{dV_{\text{col}}}{dt} = \frac{1}{\varphi} \left( \frac{g_{\text{col}} - g_{\text{col},\text{max}}}{g_{\text{col},\text{max}} - 1} \right)^2 \frac{\frac{dV_{\text{col}}}{dt}}{g_{\text{col},\text{max}} - 1} \varphi,
\]

where \( \varphi \) represents the collagen fibril deposition time. The volumetric growth in collagen fibrils (4) is bounded by the maximum \( V_{\text{col}}^{g_{\text{col},\text{max}}} \) and the minimum volume change \( V_{\text{col}}^{g_{\text{col},\text{min}}} \).

**Lamina Cribrosa Thickening**

To numerically describe the thickening of the LC seen in early experimental glaucoma, we adopt the concept of finite volumetric growth characterized through the multiplicative split of the deformation gradient \( F \) into an elastic \( F_e \) and a growth part \( F_g \)

\[
F = F_e F_g = F_e (1 + \frac{1}{2} \dot{D} \mathbf{S} \mathbf{D}),
\]

where \( D \) is a unit vector pointing in the thickness direction of the LC and \( \dot{D} = \frac{dV}{dt} \mathbf{D} \mathbf{S} \mathbf{D} \) represents the change in bulk tissue volume from the initial to the grown configuration. Following the volume fractions concept, we derive the volumetric growth of the bulk tissue material \( J \) from the change in collagen fibril volume (4)

\[
J_g = J_{g}^{\text{col}} + J_{g}^{\text{con}} + J_{g}^{\text{mat}}
\]

where \( J_{g}^{\text{col}} \), \( J_{g}^{\text{con}} \), and \( J_{g}^{\text{mat}} \) are the volume fractions of the collagen fibrils, axon bundles and matrix material at the initial configuration of the tissue, respectively. The change in collagen fibril volume (4) will also impacts the constitutive equation, where the strain energy content throughout the LC.

**RESULTS**

The presented G&R formulation was applied to a generic, axisymmetric finite element model of the human eye [6] subjected to normal (15 mmHg) and elevated IOP (25 mmHg). The model included the sclera, the pia matter and the tissues within the neural canal, where the G&R rules were only applied to the latter tissues. Starting with a uniform initial collagen fibril content (n_c=6%) throughout the neural canal tissues, the G&R algorithm created a LC-like structure at normal IO}p that partially inserted into the pia (Figure 1). At elevated IOP, the simulation remodeled the structure of the LC as follows to maintain the homeostasis at normal IOP after IOP elevation (25 mmHg). Evolution of (top row) the collagen fibril volume fraction \( n_c^{\text{col}} \) and (bottom row) the residual stretch \( \lambda_g \). The surfaces of the LC were defined as those that enclose the neural canal tissue volume with a collagen fibril volume fraction \( n_c^{\text{col}} \) of 10% or more.

**DISCUSSION**

The G&R algorithm created a LC-like structure at normal IOP and as such provided evidence in support of the biomechanical need for a LC in humans. The numerical results suggest that IOP elevation leads to LC thickening due to an increase in collagen fibril mass. Furthermore, the numerical model predicted the outward migration of the posterior LC surface. Both of these findings are consistent with observations in early experimental glaucoma monkey eyes [1,2]. However, in contrast with the experimental evidence, the G&R simulation did not predict the outward migration of the anterior LC surface nor an increased cupping of LC at elevated IOP. This inconsistency suggests that there may be additional factors, such as the biological availability of nutrients or growth factors that need to be incorporated into the G&R algorithm to capture all aspects of the LC morphologic changes seen in early experimental glaucoma.

In conclusion, this is the first study to demonstrate that a biomechanically-driven G&R mechanism can lead to the LC thickening and migration observed in early experimental glaucoma.

**REFERENCES**