Lamina Cribrosa Thickening in Early Glaucoma Predicted by a Microstructure Motivated Growth and Remodeling Approach

Rafael Grytz, Ian A. Sigal, Jeffrey W. Ruberti, Günther Meschke, J. Crawford Downs

Abstract

Glaucoma is among the leading causes of blindness worldwide. The ocular disease is characterized by irreversible damage of the retinal ganglion cell axons at the level of the lamina cribrosa (LC). The LC is a porous, connective tissue structure whose function is unclear, but is believed to provide mechanical support to the axons as they leave the eye on their path from the retina to the brain. Early experimental glaucoma studies have shown that the LC remodels into a thicker, more posterior structure which incorporates more connective tissue after intraocular pressure (IOP) elevation. The process by which this occurs is unknown. Here we present a microstructure motivated growth and remodeling (G&R) formulation to explore a potential mechanism of these structural changes. We hypothesize that the mechanical strain experienced by the collagen fibrils in the LC stimulates the G&R response at the micro-scale. The proposed G&R algorithm controls collagen fibril synthesis/degradation and adapts the residual strains between collagen fibrils and the surrounding tissue to achieve biomechanical homeostasis. The G&R algorithm was applied to a generic finite element model of the human eye subjected to normal and elevated IOP. The G&R simulation predicted the biomechanical necessity of a LC at normal IOP. The numerical results suggest that IOP elevation leads to LC thickening due to an increase in collagen fibril mass, which is in good agreement with experimental observations in early glaucoma monkey eyes. 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.

Keywords: Glaucoma, Lamina Cribrosa, Growth, Remodeling, Residual Strains, Crimped Collagen Fibrils, Optic Nerve Head

1. 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 a porous, connective tissue structure whose function 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 at the ONH. Experiments have shown that inducing elevated intraocular pressure (IOP) leads to many of the structural changes in the eye associated with early stages of the potentially blinding disease glaucoma (Figures 1, 2). It was shown that chronic intraocular IOP elevations in monkey eyes result in several structural changes in the LC: (i) overall thickening of the LC (20 to 61 µm, Yang et al., 2007, 2010a); (ii) increased LC cupping (25 to 233 µm, Yang et al., 2007, 2010a); (iii) increase in connective tissue volume (44% to 82%, Roberts et al., 2009); (iv) increased number of laminar beams through the LC thickness (17% to 48%, Roberts et al., 2009); (v) outward migration of the posterior LC surface (Yang et al., 2010b); and (vi) less pronounced outward migration of the anterior LC surface (Yang et al., 2010b). 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. The study in this paper presents a first approach...
to computational predict the biomechanical necessity of the LC and to simulate its G&R during the development of glaucoma. The aim of this paper is to derive a computational G&R formulation capable of predicting the structural changes seen in the earliest stage of experimental glaucoma. In the last decade many computational formulation have been developed to model finite growth of soft tissues (Epstein and Maugin, 2000; Lubarda and Hoger, 2002; Göktepe et al., 2010; Himpel et al., 2005; Klisch et al., 2003; Kuhl et al., 2007), and their findings were recently summarized by Ambrosi et al. (2011). While existing numerical models can simulate finite growth of soft tissues by means of the kinematic growth of finite elements, to the best knowledge of the authors, tissue migration across finite element borders has not been modeled. This is important because tissue migration is believed to be a key component of the G&R process of the LC during the earliest stages of glaucoma (Roberts et al., 2009; Yang et al., 2010b; Downs et al., 2010). To numerically model tissue migration, a mixture-based constitutive formulation is incorporated and the growth process is consistently introduced at both the kinematic and constitutive levels in accordance with the work of Schmid et al. (2011). Tissue growth is thus the result of a balance between the synthesis and degradation of collagen fibrils. Note that our model has a fundamental difference from previous work in that we do not presuppose the existence of a LC. The model allows for collagen fibrils to develop anywhere within the neural canal (or not). Thus the existence of a region with high collagenous content, which we identify as LC, is a prediction of the model and not an assumption.

Most existing formulations motivate the G&R process from an imbalance in mechanical stress or strain at the macro-scale. Flynn et al. (2010) showed recently that the mechanical strain experienced by the collagen fibrils protects the fibrils from enzymatic degradation. We thus propose a stimulus function consistent with this experimental finding, where the G&R process is driven by the mechanical stretch experienced by collagen fibril at the micro-level. The collagen fibril stretch is assumed to differ from the tissue stretch measured at the macro-scale due to residual strains (Watton et al., 2009b) and collagen fibril crimping (Grytz and Meschke, 2009). Collagen fibrils are constantly removed and deposited in the LC, which in turn may introduce residual strains between collagen fibrils and the surrounding bulk tissue. Similar to Watton et al. (2009b), we propose a remodeling rule for the adaptation of the residual stretch between collagen fibrils and the bulk tissue material in addition to the changing collagen fibril mass.

In Section 2 of this manuscript we present the theoretical framework of the proposed G&R algorithm. In Section 3 we apply the algorithm to a generic finite element model of the human eye. We conclude in Section 4 with a discussion of the algorithm, the results and the model limitations.
2. Lamina Cribrosa Growth and Remodeling

In this section a G&R approach is derived to simulate the structural changes of the LC seen during the earliest stages of experimental glaucoma. Collagen fibrils are thought to be constantly removed and deposited in the LC. We hypothesize that an upregulated synthesis or downregulated degradation of collagen fibrils may alter the collagen content and cause the volumetric growth of the LC seen in early experimental glaucoma. LC thickening is thus assumed to be a consequence of collagen fibril mass increase stimulated by the elastic stretch experienced by the collagen fibril material.

2.1. Growth and Remodeling Stimulus

In accordance with Flynn et al. (2010), 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 criterion is based on the idea that G&R occurs in an effort to maintain a homeostatic stretch environment $\lambda_{hom}$ at the collagen fibril level

$$\phi = \lambda_{fib} - \lambda_{hom}.$$  \hspace{1cm} (1)

It is unclear how deviations from this homeostatic state are sensed and eventually trigger the changes that result in the tissue’s attempt to restore homeostasis.

2.2. Collagen Fibril Crimp and Residual Strains

At the micro-scale, collagen fibrils may crimp or buckle. We derived the constitutive response of a helically crimped collagen fibril in Grytz and Meschke (2009) and estimated its 1-dimensional strain energy contribution $W^{fib}(\lambda_{axial})$ as a function of the axial stretch of the helix. The collagen fibril will uncrimp and stretch when subjected to a load in the axial direction $e_0$ of the helix. Within the crimped collagen fibril model the axial stretch is multiplicative decomposed into a part $\lambda_{crimp}$ representing the geometrical (un-)crimping of the fibril and the elastic stretch of the fibril material $\lambda_{fib}$ (Note that $\lambda_{axial}$, $\lambda_{fib}$ and $\lambda_{crimp}$ were named $\lambda_H$, $\lambda_L$ and $\lambda_\hat{H}$, respectively, in the original paper Grytz and Meschke, 2009)

$$\lambda_{axial} = \lambda_{fib} \lambda_{crimp}.$$  \hspace{1cm} (2)

Collagen fibril turnover may lead to residual strains between the collagen fibrils and its surrounding matrix material. Therefore, we introduce the residual stretch $\lambda_R$ that links the axial stretch $\lambda_{axial}$ of the crimped collagen fibril to the elastic stretch experienced by the surrounding matrix material $\lambda_{mat}$ and the axon bundles.

Figure 3: Micro-level: the crimped collagen fibril; meso-level: the collagen architecture represented by distributed collagen fibril orientations $e_0$; macro-level: the human eye model (adapted from Sigal, 2009) and the ONH region. Due to residual stretch $\lambda_R$, the stretch level in the axial direction of the collagen fibril $\lambda_{axial}$ can be higher or lower compared to macroscopic elastic stretch $\lambda_e$. Due to collagen fibril crimping $\lambda_{crimp}$, the absolute elastic strain experienced by the collagen fibril material $|\lambda_{fib} - 1|$ is always lower compared to the strain in the fibril’s axial direction $|\lambda_{axial} - 1|$. 
\[ \lambda = \lambda^\text{axon} = \lambda^\text{mat} = \lambda^\text{axial} \]  

Note that the residual stretch \( \lambda_R \) is similar to the recruitment stretch previously introduced by Watton et al. (2009b). However, in contrast to Watton et al. (2009b), we assume that collagen fibrils can bear load under compression as the helical crimp model predicts a very low stiffness of collagen fibrils under compression without loss of convexity. Figure 3 illustrates the implication of equations (2) and (3). The residual stretch is only required to be positive (\( \lambda_R > 0 \)). According to (2), the axial stretch of the collagen fibril \( \lambda^\text{axial} \) may be lower or higher compared to the macroscopic elastic stretch \( \lambda_e \) due to residual strains. In contrast, the crimping stretch is bounded by the axial stretch (1 \( \leq \lambda^\text{crimp} \leq \lambda^\text{axial} \geq 1 \) and \( \lambda^\text{axial} \geq \lambda^\text{crimp} \geq 1 \)). By the so-called locking stretch (\( \lambda^\text{lock} = 1/(\cos \theta) \)) through the boundary value problem at the micro-level (Grytz and Meschke, 2009). Consequently, the absolute strain level experienced by the collagen fibril material is always lower compared to the absolute strain in the fibril’s axial direction \( |\lambda^\text{axial} - 1| \). It is often suggested that residual strains evolve mainly due to the continuous synthesis and degradation of collagen fibrils while the tissue is subjected to external loading (Kroon, 2010). Foonen et al. (2010) demonstrated that chicken embryo periosteum resides in a homeostatic mechanical state, which is characterized by a residual strain that corresponds to the belly region of the stress-strain curve of the tissue. They demonstrated that this homeostatic state was regained upon strain perturbation. In contrast to the common assumption, this remodeling phenomena did not depend on protein synthesis, because the addition of cycloheximide did not affect the response. In light of this evidence, we decided to formulate an independent evolution equation for the residual stretch \( \lambda_R \) rather than relating it to the collagen fibril synthesis and degradation derived in the following subsection. We propose a simple linear differential equation for the evolution of \( \lambda_R \):

\[
\frac{d\lambda_R}{dt} = \frac{1}{\tau_R} \phi, \tag{4}
\]

where the homeostatic mechanical state is defined at the micro-level through the stimulus function \( \phi \) in (1). The parameter \( \tau_R \) in (4) relates to the remodeling time needed to achieve homeostasis.

### 2.3. 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 \( \mathbf{F} \) into an elastic \( \mathbf{F}_e \) and a growth part \( \mathbf{F}_g \) (Rodriguez et al., 1994):

\[
\mathbf{F} = \mathbf{F}_e \mathbf{F}_g. \tag{5}
\]

The volume change of a differential volume element is defined by the determinate of \( \mathbf{F} \) which can be also split according to (5) into elastic and growth related volume changes:

\[
J = \frac{dV}{dV_0} = \det \mathbf{F}_e \det \mathbf{F}_g = \frac{dV}{dV_0} = J_e J_g. \tag{6}
\]

Here, the volume elements \( dV, dV_g \) and \( dV_0 \) relate to the current \( \mathcal{B} \), the grown (or intermediate) \( \mathcal{B}_g \) and the reference configuration \( \mathcal{B}_0 \) of the LC tissue.

Let \( \mathbf{M}_1 \) be an orthonormal basis defined in the reference configuration of the body \( \mathcal{B}_0 \), where \( \mathbf{M}_3 \) points into the thickness direction of the LC. A dedicated thickening of the LC can be introduced by specifying the growth tensor as follows:

\[
\mathbf{F}_g = \mathbf{I} + (\lambda_g - 1) \mathbf{M}_3 \otimes \mathbf{M}_3, \tag{7}
\]

where \( \lambda_g \) represents a growth multiplier of the tissue volume. Pure elastic deformations are represented by \( \lambda_e = 1 \) while LC shrinkage occur for \( \lambda_g < 1 \) and LC thickening for \( \lambda_g > 1 \). One can easily relate the Jacobian of the growth tensor to the growth multiplier as:

\[
J_g = \det \mathbf{F}_g = \lambda_g. \tag{8}
\]

### 2.4. Lamina Cribrosa Constituents

The LC is traditionally defined by its porous collagen architecture through which axon bundles exit the eye. Astrocytes and other cells are present to maintain the tissue functionality. We assume that the LC tissue volume includes three constituents, which we treat as solids: (i) the collagen fibril architecture; (ii) the axon bundles and (iii) the surrounding matrix material, which includes cells, elastin and other extracellular matrix components. Following the volume fractions concept, we introduce the initial volume fractions \( n^0_c \), which refer the volume element \( dV_0^c \) of each constituent (\( c = \text{col}, \text{axon}, \text{mat} \)) to the bulk tissue volume element \( dV_0 \) at the initial configuration \( \mathcal{B}_0 \):

\[
n^0_c = \frac{dV_0^c}{dV_0}. \tag{9}
\]

The volume occupied by collagen fibrils may change due to changes in collagen fibril synthesis or degradation as will be derived in Subsection 2.5. This change in
collagen fibril volume from the initial \( V_0 \) to the (intermediate) grown configuration \( V_g \) is represented by the growth Jacobian \( J_g \):

\[
J_g = \frac{dV_g}{dV_0}.
\]

Following the derivations of Schmid et al. (2011) the volumetric growth of the bulk material \( J_g \) (8) can be redefined by the growth Jacobians of its constituents:

\[
J_g = \frac{dV_g}{dV_0} = \sum_a \frac{dV_a}{dV_0} = \sum_a \frac{dV_a}{dV_0} \frac{dV_0}{dV_0} = \sum_a J_a^n(11)
\]

Equation (11) can be further simplified as we assume that the volume occupied by the axon bundles and the matrix material remain constant during the growth process:

\[
J_g = J_g^{col} n_0^{axon} + J_g^{axon} + J_g^{mat}.
\]

Note that relation (12) links the volume change of the collagen fibril architecture (10) to the kinematic thickening of the LC bulk material (7) through (8) (see illustration in Figure 4).

Changes in the volume occupied by the collagen fibril architecture (10) will lead to a new mixture with modified volume fractions for all three constituents. At the grown configuration the volume fractions can be derived from (9), (10) and (11):

\[
n_g^a = \frac{dV_g^a}{dV_g} = \frac{n_g^a}{n_0^a} = \frac{dV_g^a}{dV_0^a} \frac{dV_0^a}{dV_g} = J_g^a n_0^a.
\]

Note that at any time the sum of volume fractions satisfies the volume fraction condition:

\[
n_g^{col} + n_g^{axon} + n_0^{mat} = n_g^{col} + n_g^{axon} + n_0^{mat} = 1.\]

2.5. Collagen Fibril Synthesis and Degradation

Experimental studies revealed that the mechanical environment of soft tissues may impact both the synthesis and degradation of collagen fibrils (Flynn et al., 2010; Wang and Thampattty, 2006). Due to changes in collagen fibril synthesis and degradation, the number of collagen fibrils per unit bulk volume may change from \( N_0^{fib} \) at time \( t_0 \) to \( N^{fib} \) at time \( t \). If the mass of one collagen fibril \( m_0^{fib} \) remains constant in time, the change in collagen fibril mass density may be approximated by the change in the volume occupied by the collagen fibril architecture as assumed here:

\[
\frac{N_0^{fib} m_0^{fib}}{N^{fib} m_0^{fib}} = \frac{dV_g^{col}}{dV_0} = J_g^{col}.
\]

We introduce a simple evolution equation for the growth Jacobian of the collagen fibril architecture \( J_g^{col} \) to model the changing collagen fibril synthesis and degradation stimulated by the criterion \( \phi \):

\[
\frac{dJ_g^{col}}{dt} = k^{col} \phi.
\]

The volumetric growth in collagen fibrils is weighted by the function \( k^{col} \):

\[
k^{col} = \frac{1}{\tau_g} \left[ \frac{J_g^{col}}{J_g^{col, max}} - 1 \right]^2 \left[ \frac{J_g^{col} - J_g^{col, min}}{J_g^{col, max} - J_g^{col, min}} \right]^2
\]

where \( \tau_g \) represents the collagen fibril deposition time.

To assure the functionality of LC, we assume that the volumetric growth in collagen fibrils is constrained such that enough volume is left for the axon bundles to pass through the collagen fibril architecture and that not all collagen fibrils vanish. Therefore, the volumetric growth in collagen fibrils \( k^{col} \) is bounded by the maximal \( J_g^{col, max} \) and the minimal volumetric change \( J_g^{col, min} \) in (17). Note that while the stimulus \( \phi \) in the evolution equation (16) is based on the microstructure of collagen fibrils, the weighting function \( k^{col} \) is phenomenologically motivated.
2.6. Constitutive Equations

The increase or decrease in collagen fibril mass will change the composition of LC constituents and, therefore, also impact the strain energy density of the LC bulk material $W$. We assume that the strain energy contribution $W^a$ of each constituent ($\alpha=\text{col}, \text{axon}, \text{mat}$) is linearly dependent on its volume fraction $n^a_\alpha$ defined at the grown configuration $\mathcal{B}_g$,

$$ W = \sum_\alpha n^a_\alpha W^a + U, \quad (18) $$

where $U$ represents the volumetric energy contribution of the bulk material. The tissue strain energy density can be reformulated by using (13) and incorporating the growth Jacobian of the collagen architecture $J^\text{col}_G$ and the bulk LC material $J_g$,

$$ W = \sum_\alpha n^a_\alpha n^0_\alpha W^a + U = \sum_\alpha \frac{J^\text{col}_G}{J_g} n^0_\alpha W^a + U $$

$$ = \frac{J^\text{col}_G}{J_g} n^0_\alpha W^\text{col} + \frac{J^\text{axon}_G}{J_g} W^\text{axon} + \frac{J^\text{mat}_G}{J_g} W^\text{mat} + U. $$

Let us assume that the strain energy density $W$ stored in the tissue can be characterized in terms of the elastic right Cauchy-Green tensor

$$ C_e = F^e F_e = F^e T C F_e^{-1}. \quad (20) $$

It was previously shown that the second Piola-Kirchhoff stress $S$ is thermodynamically conjugated to the right Cauchy-Green tensor $C = F^T F$ and can be interpreted as the pull back of the elastic stress tensor $S_e$ from the grown $\mathcal{B}_g$ to the reference configuration $\mathcal{B}_0$,

$$ S = 2\frac{\partial W(C_e)}{\partial C_e} = F^{-1}_e S_e F^{-1}_e T \quad \text{with} \quad S_e = 2\frac{\partial W(C_e)}{\partial C_e}. \quad (21) $$

For detailed derivations and extensive discussions on open system thermodynamics we refer to the literature (Epstein and Maugin, 2000; Lubarda and Hoger, 2002; Kuhl and Steinmann, 2003; Himpe1 et al., 2005).

The strain energy function of the matrix material is approximated by means of an isochoric Neo-Hookean formulation

$$ W^\text{mat}(C_e) = \frac{1}{2} \mu (J_e^{2/3} \text{tr} C_e) \quad (22) $$

with the shear modulus $\mu$. While the isochoric energy contribution of the axon bundles is assumed to be negligible $W^\text{axon} = 0$, its volumetric contribution is indirectly considered through $U$ representing the volumetric response of the bulk material of the mixture

$$ U(J_e) = \frac{1}{2} K (\ln J_e)^2, \quad (23) $$

where $K$ is the bulk modulus.

Following our previous work (Grytz, 2008; Grytz and Meschke, 2010), the collagen fibril architecture is represented by a generalized structure tensor

$$ H = \kappa M_1 \otimes M_1 + (1 - \kappa) M_2 \otimes M_2. \quad (24) $$

where collagen fibril orientations $e_0$ were assumed to be normal distributed around $M_1$ in the plane spanned by $M_1$ and $M_2$. The mesostructural parameter $\kappa$ represents the collagen fibril dispersion in an integral sense. Roberts et al. (2009) reported that the anisotropic collagen fibril dispersion of the LC does not change during early experimental glaucoma. Accordingly, the generalized structure tensor (24) is assumed to be constant in time.

If we, furthermore, assume constant residual stretch values $\lambda_R$ in all fibril orientation $e_0$, the overall elastic stretch of the collagen architecture can be approximated as

$$ \lambda^{\text{col}} = \frac{\sqrt{C^e : H}}{\lambda_R} = \frac{\sqrt{C : H}}{\lambda_R}. \quad (25) $$

Note that due to the dedicated growth of the LC in its thickness direction $M_3$ assumed by the growth tensor in (7), the elastic stretch of the collagen architecture can be directly computed by using $C$ in (25). The strain energy contribution of the collagen architecture is approximated by the energy function derived in Grytz and Meschke (2009) for one crimed collagen fibril as a function of the overall collagen stretch

$$ W^{\text{col}} = W^{\text{fib}}(\lambda^{\text{axial}} = \lambda^{\text{col}}(C, H, \lambda_R)). \quad (26) $$

Note that the solution of (26) will provide both the current constitutive response of the collagen fibril architecture and the collagen fibril stretch $\lambda^{\text{fib}}$ used in (1) to define the G&R stimulus.

3. Numerical Example

The G&R formulation presented in Section 2.1 is now applied to a generic, axisymmetric finite element model of the human ONH.

3.1. Finite element model of the human optic nerve head

The geometry of the eye model was adapted from a previously described parametric model and includes the sclera, the neural canal tissues and the pia mater (Figure 5; for dimensions see base-line model in Sigal et al.,...
The neural tissue anteriorly to the modeled neural canal tissues was assumed to be unable to incorporate a LC-like structure and was therefore disregarded in the model. A $10^\circ$ piece of the axisymmetric eye model was discretized into 4002 hexahedral finite elements and standard axisymmetric boundary conditions were applied (Figure 5a, c). The 20-node quadratic element formulation is based on a reduced integration scheme provided by the commercial finite element suite ABAQUS (Ver. 6.8, Hibbitt, Karlsson & Sorensen, Inc., Providence, RI). The preferred collagen fibril orientations $M_1$ are shown in Figure 5b. Collagen fibrils were assumed to be isotropically dispersed in all tissues except for the highly aligned ring of fibrils in the peripapillary scleral ring region surrounding the scleral canal. The peripapillary ring of collagen fibrils has been shown histologically (Hernandez et al., 1987; Morrison et al., 1989) and by using second harmonic imagining techniques (Winkler et al., 2010). The biomechanical advantages of the peripapillary fibril ring and its implication on the stress environment of LC were previously discussed in Grytz et al. (2010); Girard et al. (2009).

The strain energy contributions $W_{\text{col}}$ and $W_{\text{mat}}$ were assumed to represent the energy contribution of basic tissue constituents, in particular, the collagen fibril architecture and its surrounding matrix material. Consequently, the constitutive parameters of $W_{\text{mat}}$ and $W_{\text{col}}$ summarized in Table 1 were assumed to be constant in all the tissues of the eye model and tissue-specific differences in the hyperelastic response were exclusively introduced by tissue-specific volume fractions and the collagen fibril dispersion. The bulk modulus was set to 0.2 MPa for the neural canal tissues and 2.0 MPa for the other tissues. The initial volume fractions are summarized in Table 2.

### Table 1: Global constitutive parameters of the strain energy functions (SEF) $W_{\text{mat}}$ and $W_{\text{col}}$ used in (19).

<table>
<thead>
<tr>
<th>SEF</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W_{\text{mat}}$</td>
<td>Shear modulus of the matrix material per $dV_{\text{mat}}^0$</td>
<td>$\mu = 0.05$ MPa</td>
</tr>
<tr>
<td>$W_{\text{col}}$</td>
<td>Elastic modulus of collagen fibrils per $dV_{\text{col}}^0$</td>
<td>$E = 62.4$ MPa</td>
</tr>
<tr>
<td>$W_{\text{col}}$</td>
<td>Collagen fibril crimp angle*</td>
<td>$\theta_0 = 5.09^\circ$</td>
</tr>
<tr>
<td>$W_{\text{col}}$</td>
<td>Ratio between the radii of the helix and fibril*</td>
<td>$R_0/r_0 = 1.04$</td>
</tr>
</tbody>
</table>

* Illustrated in Figure 3 (micro-level).

### Table 2: Initial volume fractions.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$n_{\text{col}}^0$</th>
<th>$n_{\text{mat}}^0$</th>
<th>$n_{\text{axon}}^0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclera</td>
<td>0.6</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Pia</td>
<td>0.6</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Neural canal tissues</td>
<td>0.06*</td>
<td>0.235</td>
<td>0.705</td>
</tr>
</tbody>
</table>

* Note that the neural canal tissues were not assumed to have a LC at the initial configuration $B_0$. 

Figure 5: (a) Finite element mesh of the generic axisymmetric model including a detailed view of the ONH region showing the peripapillary scera, the peripapillary scleral ring tissue, the pia mater and the neural canal tissues. (b) Exploded view of the ONH region showing the preferred collagen fibril orientations $M_1$ (black arrows) and the collagen fibril dispersion parameter $\kappa$. 

---

2005). The neural tissue anteriorly to the modeled neural canal tissues was assumed to be unable to incorporate a LC-like structure and was therefore disregarded in the model. A $10^\circ$ piece of the axisymmetric eye model was discretized into 4002 hexahedral finite elements and standard axisymmetric boundary conditions were applied (Figure 5a, c). The 20-node quadratic element formulation is based on a reduced integration scheme provided by the commercial finite element suite ABAQUS (Ver. 6.8, Hibbitt, Karlsson & Sorensen, Inc., Providence, RI). The preferred collagen fibril orientations $M_1$ are shown in Figure 5b. Collagen fibrils were assumed to be isotropically dispersed in all tissues except for the highly aligned ring of fibrils in the peripapillary scleral ring region surrounding the scleral canal. The peripapillary ring of collagen fibrils has been shown histologically (Hernandez et al., 1987; Morrison et al., 1989) and by using second harmonic imagining techniques (Winkler et al., 2010). The biomechanical advantages of the peripapillary fibril ring and its implication on the stress environment of LC were previously discussed in Grytz et al. (2010); Girard et al. (2009).
The G&R rules outlined in Section 2.1 were exclusively applied to the tissues within the neural canal. Volumetric growth of the collagen fibril architecture was limited by the maximal \( F_{col}^{\text{max}} = 3.92 \) and minimal volume change \( F_{col}^{\text{min}} = 0.0016 \) through (17) restricting the volume fraction of collagen fibrils to be between 20% and 0.01%. The temporal discretization of the evolution equations (4) and (16) was realized by the explicit update of the collagen fibril volume fraction \( n_{col} \) and the residual stretch \( \lambda_R \). Due to their phenomenological nature, the time constants controlling the speed of the G&R process are given with respect to not further specified time units (TU). These time constants were set to \( \tau_R = 1.0 \) TU and \( \tau_\text{s} = 0.01 \) TU. Time increments were kept reasonably small to prevent numerical oscillation during the G&R simulation. The homeostatic collagen fibril stretch was estimated to \( \lambda_{\text{hom}} = 1.001 \).

This fibril stretch relates to the tissue stretch that corresponds to the beginning of the belly region of the tissue stress-stretch curve similar to the homeostatic mechanical state in chicken embryo periosteum observed by Foolen et al. (2010).

At \( t = t_0 = 0 \) the simulation started with a uniform initial collagen fibril content throughout the neural canal tissues and IOP was quasi-instantly increased to a normal value of 15 mmHg. Then, IOP was held constant and the G&R rules were applied until homeostasis was achieved at \( t = t_1 = 300 \) TU. Thereafter IOP was (quasi instantly) elevated to 25 mmHg. Due to G&R, homeostasis was again achieved at elevated IOP at \( t = t_3 = 600 \) TU.

### 3.2. Numerical results

Selected numerical results of the G&R simulation showing the evolution of the LC at time \( t = t_0, t_1, t_2 \) are presented in Figure 6. We assume that neural canal tissues with a collagen fibril volume fraction \( n_{col} \) of 10% or more represents the LC, while tissues with less than 10% collagen fibril volume fraction represent pre- and retro-laminar tissue. At \( t = t_0 \) the normal IOP level (15 mmHg) was applied to the initial eye model considering uniform collagen fibril content throughout the neural canal tissues. Due to the pressure loading, collagen fibrils were overstretched \( (\lambda_{\text{fib}} > \lambda_{\text{hom}}) \) across the scleral canal as can be seen in bottom left of Figure 6. This in turn stimulated the G&R algorithm to increase collagen fibril mass across the scleral canal while decreasing it in pre- and retro-laminar regions. At \( t = t_1 \), all collagen fibrils within the neural canal reached the hypothesized homeostasis and a LC-like structure that spans across the scleral canal was created by the G&R algorithm. The residual stretch was minimal at \( t = t_1 \).

### 4. Discussion and Limitations

A numerical G&R algorithm was presented for soft biological tissues to model tissue growth and migration induced by changing collagen fibril synthesis and degradation. Tissue migration was numerically accomplished by incorporating a mixture-based constitutive formulation and introducing the growth process consistently at both the kinematic and constitutive level as suggested by Schmid et al. (2011).

The proposed G&R algorithm was applied to a generic finite element model of the human ONH with uniform initial collagen content throughout the tissues within the neural canal, and allowed to achieve homeostasis at normal (15 mmHg) and elevated IOP (25 mmHg). At normal IOP, the G&R algorithm created a LC-like structure that spanned the scleral canal and as such confirmed the biomechanical necessity of a LC in humans. At elevated IOP, the simulation remodeled

### Table 3: Structural changes in the LC due to IOP elevation from 15 mmHg to 25 mmHg predicted by the G&R simulation. The LC was defined as neural canal tissue with a collagen fibril volume fraction \( n_{col} \) of 10% or more.

<table>
<thead>
<tr>
<th>IOP</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mmHg</td>
<td></td>
</tr>
<tr>
<td>Bulk tissue volume</td>
<td>0.70 ( \mu l )</td>
</tr>
<tr>
<td>Total collagen fibril volume</td>
<td>95 ( \mu l )</td>
</tr>
<tr>
<td>Overall collagen fibril volume fraction</td>
<td>13.7%</td>
</tr>
<tr>
<td>LC central thickness</td>
<td>167 ( \mu m )</td>
</tr>
<tr>
<td>LC thickness at scleral insertion</td>
<td>275 ( \mu m )</td>
</tr>
<tr>
<td>25 mmHg</td>
<td></td>
</tr>
<tr>
<td>Bulk tissue volume</td>
<td>1.06 ( \mu l )</td>
</tr>
<tr>
<td>Total collagen fibril volume</td>
<td>155 ( \mu l )</td>
</tr>
<tr>
<td>Overall collagen fibril volume fraction</td>
<td>14.8%</td>
</tr>
<tr>
<td>LC central thickness</td>
<td>250 ( \mu m )</td>
</tr>
<tr>
<td>LC thickness at scleral insertion</td>
<td>359 ( \mu m )</td>
</tr>
</tbody>
</table>

An IOP elevation to 25 mmHg reactivated the G&R process, which resulted in LC thickening and migration. Characteristic structural changes of LC that developed during the early glaucoma G&R simulation are presented in Table 3. The LC thickness increased by 50% at the center and 30% at the insertion of the LC into the sclera and pia. This thickening resulted partially from a higher collagen fibril concentration in the core region of the LC but mainly from the inward and outward migration of the anterior and posterior LC surfaces, respectively. In total, the collagen fibril volume in the LC increased by 63% from \( t_1 \) to \( t_2 \) while the LC bulk tissue volume increased by 52%. Residual stretch evolved locally with the maximal value \( \lambda_{R,max} = 1.02 \) near the region, where the LC, sclera, pia and optic nerve meet.
Figure 6: G&R simulation results showing the neural canal tissues, the peripapillary sclera, the pia matter, and the evolution of the LC at time $t = t_0, t_1, t_2$. Left column ($t = t_0$): model with initial uniform collagen content throughout the tissues within the neural canal subjected to normal IOP (15 mmHg). Middle column ($t = t_1$): model homeostasis at normal IOP (15 mmHg). Right column ($t = t_2$): model homeostasis after IOP elevation (25 mmHg). Evolution of (top row) the collagen fibril volume fraction $n_{col}^c$; (middle row) the residual stretch $\lambda_R$; and (bottom row) the collagen fibril stretch $\lambda_{fib}$. The surfaces of the LC were defined as those that enclose the neural canal tissue volume with a collagen fibril volume fraction $n_{col}^c$ of 10% or more.
the structure of the LC as follows to maintain the hypothesized homeostatic state: (i) 63% increase in collagen fibril volume; (ii) up to 2% increase in local residual strain; (iii) 52% increase in LC volume; (iv) 40% increase in LC thickness; (v) inward migration of the anterior LC surface and (vi) outward migration of the posterior LC surface that resulted in further insertion of the LC into the pia mater.

The bulk LC tissue volumes predicted by the G&R algorithm at normal (0.7 nl) and elevated IOP (1.06 nl) are in very good agreement with the range of volumes (0.49 nl to 1.15 nl) obtained from three-dimensionally reconstructed human LCs by Sigal et al. (2010). Roberts et al. (2009) reported that the connective tissue volume in early glaucoma monkey eyes compared to contralateral normals increased significantly (82%, 44% and 45%) but the average connective tissue volume fraction changed little (-7%, 1% and -2%). The significant increase in collagen fibril volume (63%) and the little change in collagen fibril volume fraction (8%) due to IOP elevation predicted by the G&R simulation are in good agreement with these experimental results. Yang et al. (2007) observed for three monkeys the consistent thickening of the LC during the earliest stages of experimental glaucoma (59%, 18% and 31%). The numerically predicted thickening of the LC at its center (50%) and at the LC insertion (30.5%) is in very good agreement with this experimental evidence. Yang et al. (2010b) recently observed the outward migration of the posterior LC surface in 9 early experimental glaucoma monkey eyes compared to their contralateral normal eyes. 3 out of the 9 early experimental glaucoma eyes demonstrated an outward migration of the LC such that the LC inserted into the pia. Also the anterior LC surface migrated outwardly but was less pronounced than the migration of the posterior surface. The numerical model predicted the outward migration of the posterior LC surface consistent with these experimental observations. In contrast to the experimental observation, the G&R simulation showed an inward migration of the anterior LC surface. This inconsistency indicates 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 the dedicated posterior migration of the LC seen in early experimental glaucoma.

The LC-like structure created by the G&R algorithm at normal IOP developed at the posterior end of the scleral canal and partially inserted into the pia mater. The insertion of the LC into the pia is present in some ostensible human normal eyes (Sigal et al., 2010) and may be a natural migration in eyes with elevated IOP (Downs et al., 2010). The predicted position of the LC insertion at normal IOP relates to the assumed initial condition of the eye model including the eye geometry, constitutive parameters and the collagen fibril architecture. Future parametric studies may reveal the relationships between the different model parameters and the numerical prediction of the LC position at normal IOP.

Glaucoma is generally associated with cupping (posterior deformation) of the ONH surface, which is clinically visible using a variety of instruments (Hernandez, 2000; Jonas et al., 2003; Ren et al., 2009). There are two components of glaucomatous cupping: the first is prelaminar cupping due to the loss of prelaminal neural tissues as axons die, and the second is laminar cupping that is due to the remodeling of the LC into a more posteriorly deformed (cupped) structure (Yang et al., 2007; Burgoyne and Downs, 2008; Downs et al., 2008, 2010; Yang et al., 2010a). While it is unclear how extensive laminar cupping is in human glaucoma, LC cupping has been shown to accompany LC thickening in early experimental glaucoma in the non-human primate (Yang et al., 2007, 2010a). The G&R simulation results presented herein do not predict significant LC cupping at elevated IOP, which could be related to the model’s inability to capture a dedicated posterior movement as discussed in the previous paragraph. However, we observed that increasing the ratio \( \tau_\sigma/\tau_\delta \), which relates to the ratio between the residual strain adaptation speed to collagen fibril deposition time, increases LC cupping while simultaneously decreases LC thickening in the G&R simulation. Still, there may be additional factors that need to be incorporated into the algorithm to fully capture the glaucomatous changes in LC morphology.

Based on a microstructure-motivated constitutive formulation for crimped collagen fibrils, the G&R stimulus was traced back to the collagen fibril stretch based on recent experimental evidence of collagen fibril degradation mechanisms (Flynn et al., 2010). In contrast to classical G&R approaches based on macroscopic strain or stretch stimuli, the microstructure-motivated stimulus proposed here decouples geometric effects, such as collagen fibril uncrimping and residual strains, from the hypothesized homeostatic biomechanical state. Previous G&R formulations also incorporated a residual stretch (also called recruitment stretch) to motivate a homeostatic mechanical state at the collagen fiber level (Watton et al., 2009a; Machshyn et al., 2010). These models required for a rather high homeostatic stretch value (also called attachment stretch) \( \lambda_{\text{hom}}=1.1 \) to achieve a realistic G&R response. The latest experimental results, however, show that collagen fibrils experience much lower pre-stretch levels after synthesis.
The experiments also suggest for a much lower protective or homeostatic stretch level (Jeff, do you have a range and a paper to cite?). Incorporation of the collagen fibril crimp response in addition to the residual stretch enables the present formulation to use a more realistic (low) value for the homeostatic stretch at the fibril level $\lambda_{\text{hom}} = 1.001$, which consistent with latest experimental results.

While the major structural impact during the early glaucoma G&R simulation was achieved by controlling collagen fibril synthesis and degradation, homeostasis throughout the tissues within the neural canal was only achieved when considering the adaptation of the residual stretch. A modified simulation showed that homeostasis was not regained near the posterior scleral border when the evolution of the residual stretch was disregarded. This region of the neural canal is characterized by an IOP-induced strain concentration.

While the G&R stimulus is derived from the tissue microstructure, the parameters that control the rate of the G&R process $(\tau_R, \tau_J)$ including the limiting growth factors $\bar{J}^{\text{col}, \min}$ and $\bar{J}^{\text{col}, \max}$ are phenomenologically based and do not have a clear biological interpretation. Further development should explicitly address growth factors, enzyme and nutrients concentrations, and signaling pathways that control the maintenance of the collagen fibril architecture.

In conclusion, the presented G&R algorithm confirmed the biomechanical necessity of a LC at normal IOP. The numerical results suggest that IOP elevation may lead to LC thickening due to an increase in collagen fibril mass, which is in good agreement with latest experimental observations in early glaucoma monkey eyes. This is the first study to demonstrate that a biomechanically-driven G&R mechanism can lead to the characteristic thickening and migration of the LC seen in early glaucoma.

References


