

## MULTISCALE MODELING AND COMPUTATIONAL REMODELING OF HUMAN EYE TISSUES

Rafael Grytz and Günther Meschke\*

*\*Institute for Structural Mechanics  
Ruhr-University Bochum  
44801 Bochum, Germany*

*e-mail: rafael@grytz.de, guenther.meschke@rub.de*

*web page: <http://www.sd.rub.de>*

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**Abstract.** *A stress based remodeling approach [1] is used to investigate the sensitivity of the collagen architecture in humane eye tissues on the biomechanical response of the lamina cribrosa with a particular focus on the stress environment of the nerve fibers. This approach is based on a multi-level biomechanical framework, where the biomechanical properties of eye tissues are derived from a single crimped fibril at the micro-scale via the collagen network of distributed fibrils at the meso-scale to the incompressible and anisotropic soft tissue at the macro-scale [1,2]. Biomechanically induced remodeling of the collagen network is captured on the meso-scale by allowing for a continuous reorientation of collagen fibrils. To investigate the multi-scale phenomena related to glaucomatous neuropathy a generalized computational homogenization scheme [3] is applied to a coupled two-scale analysis of the human eye considering a numerical macro- and meso-scale model of the lamina cribrosa.*

## 1 INTRODUCTORY REMARKS

The ocular disease glaucoma is the second most common cause of blindness in the world. An abnormally elevated intraocular pressure level is the most relevant risk factor for the development of glaucoma. Present evidence indicates that damage to the optic nerve axons occurs at the level of the lamina cribrosa. This region of the optic nerve head is also known to have an increased vulnerability to an interruption of the optic nerve axonal transport caused by an elevated intraocular pressure [4–8]. In glaucomatous eyes an extensive remodeling of the extracellular matrix takes place at the lamina cribrosa. Complex, biomechanical phenomena occurring at different length scales are involved in the pathophysiology of glaucoma. Mathematical models can be of great value to gain insight into the multi-scale phenomena related to the biomechanical properties of the optic nerve head in physiological and pathophysiological conditions. Realistic computational simulation strategies of the lamina cribrosa structure at multiple scales might be a powerful tool to predict a certain risk for the development and progression of ocular diseases such as glaucoma. In this contribution, a numerical remodeling approach [1] is used to investigate the interaction between collagen fibril architecture and mechanical loading conditions in the optic nerve head region. To investigate axoplasmatic transport interruption in glaucoma a generalized computational homogenization scheme [3] is applied to a numerically coupled two-scale analysis of the human eye considering a finite element macro- and meso-scale model of the lamina cribrosa.

## 2 MICROMECHANICAL MODEL FOR SOFT COLLAGENOUS TISSUES

Our investigation starts at the micro-level, where collagen fibrils are assumed to crimp into the shape of a cylindrical helix when the tissue is unloaded (Figure 1). The constitutive response of individual fibrils is derived from the nonlinear relation between the 1. Piola-Kirchhoff fiber stress  $P_{\text{fib}}$  and the fiber stretch  $\lambda_{\text{fib}}$  of an extensible helical spring including the fully extension of the spring as a limit case [2].

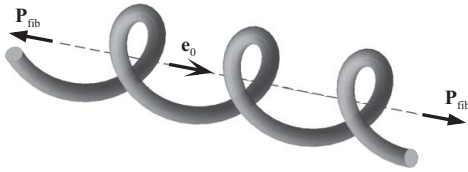


Figure 1: Reference configuration of a single crimped collagen fibril.

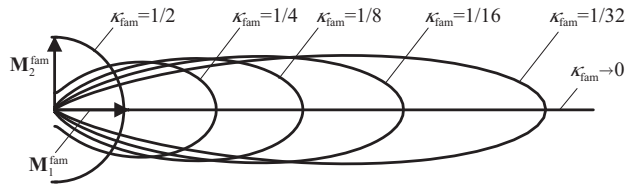


Figure 2: Graphical representation of the distributed fibril orientations  $e_0$  of one fibril family

On the meso-level, the collagen network in eye tissues is represented by means of two families of collagen fibrils. The orientations of individual collagen fibrils  $e_0$  within each family (fam $\alpha$  with  $\alpha = 1, 2$ ) is considered to be symmetrically dispersed by means of a normalized *von Mises* distribution in the plane spanned by the two vectors  $M_1^{\text{fam}\alpha}$ - $M_2^{\text{fam}\alpha}$  of the orthonormal frame  $M_j^{\text{fam}\alpha}$ , where  $M_1^{\text{fam}\alpha}$  is the mean direction (Figure 2). Following the work of Gasser et al. [9] a generalized structure tensor is introduced for each fibril family

$$\mathbf{H}_{\text{fam}\alpha} = [(1 - \kappa)\mathbf{M}_1 \otimes \mathbf{M}_1 + \kappa\mathbf{M}_2 \otimes \mathbf{M}_2]_{\text{fam}\alpha} \quad (1)$$

with a single dispersion parameter  $\kappa_{\text{fam}\alpha} \in [0; 1/2]$  representing the two-dimensional fibril dispersion in an integral sense.

On the macro-level, let the strain energy density of eye tissues be composed of an isotropic part and two anisotropic parts representing the energy contribution of the extrafibrillar matrix and of the two families of crimped collagen fibrils with dispersed orientations

$$W = c(I_C - 3) + \sum_{\alpha=1}^2 \int_1^{\sqrt{\bar{I}_C^{\text{fam}\alpha}}} P_{\text{fib}}(\lambda) d\lambda \quad \text{with } I_C = \text{tr} \mathbf{C}, \bar{I}_C^{\text{fam}\alpha} = \mathbf{H}_{\text{fam}\alpha} : \mathbf{C} \quad (2)$$

under consideration of the incompressibility constraint  $III_C = \det \mathbf{C} = 1$  in accordance to [10].

### 3 COMPUTATIONAL REMODELING OF THE COLLAGEN MESO-ARCHITECTURE

To gain further insight into the complex biomechanical phenomena related to optic nerve head remodeling, the remodeling algorithm [1, 11–13] is applied to a numerical human eye model including the peripapillary sclera and lamina cribrosa. The remodeling algorithm is stimulated by the local stress environment at the macro or tissue level. The fundamental hypothesis of the proposed remodeling theory is that the orientation of individual collagen fibrils rotate such that after remodeling the collagen network can be again characterized by two generalized structural tensors of the form (1). Accordingly, the biomechanically induced remodeling process can be decomposed into the reorientation of the orthonormal frame  $\mathbf{M}_j^{\text{fam}\alpha}$  and into the variation of the dispersion parameter  $\kappa_{\text{fam}\alpha}$  of each collagen fibril family ( $\text{fam}\alpha = 1, 2$ ). The scalar function used for the definition of the stress based remodeling stimulus is postulated as

$$\Gamma = \begin{cases} \tau_2/\tau_1 & \text{for } \tau_2 \geq 0 \\ 0 & \text{for } \tau_2 < 0. \end{cases} \quad \text{with } \boldsymbol{\tau} = \sum_{i=1}^3 \tau_i \mathbf{n}_i \otimes \mathbf{n}_i \quad \text{and } \tau_1 \geq \tau_2 \geq \tau_3 \quad (3)$$

Herein the spectral decomposition of the Kirchhoff stress tensor  $\boldsymbol{\tau}$  is introduced, where  $\tau_i$  and  $\mathbf{n}_i$  are the corresponding eigenvalues and eigenvectors, respectively. The target directions  $\mathbf{M}_j^{\text{tar}\alpha}$  of the reorientation process of  $\mathbf{M}_j^{\text{fam}\alpha}$  defined at the reference configuration are chosen such that at the current configuration all collagen fibrils tend to reorient into the  $\mathbf{n}_1$ - $\mathbf{n}_2$  plane, while the mean fibril directions will be located between  $\mathbf{n}_1$  and  $\mathbf{n}_2$  [14]

$$\begin{aligned} \mathbf{M}_1^{\text{tar}1} &= \mathbf{F}_{\triangleleft} [\cos(\arctan \Gamma) \mathbf{n}_1 + \sin(\arctan \Gamma) \mathbf{n}_2] \\ \mathbf{M}_1^{\text{tar}2} &= \mathbf{F}_{\triangleleft} [\cos(\arctan \Gamma) \mathbf{n}_1 - \sin(\arctan \Gamma) \mathbf{n}_2] \\ \mathbf{M}_2^{\text{tar}\alpha} &= \mathbf{M}_3^{\text{tar}\alpha} \times \mathbf{M}_1^{\text{tar}\alpha}, \quad \mathbf{M}_3^{\text{tar}\alpha} = \mathbf{n}_3 \mathbf{F} / \|\mathbf{n}_3 \mathbf{F}\| \end{aligned} \quad \text{with } \mathbf{M} = \mathbf{F}_{\triangleleft}(\mathbf{m}) = \frac{\mathbf{F}^{-1} \mathbf{m}}{\|\mathbf{F}^{-1} \mathbf{m}\|}. \quad (4)$$

The temporal evolution of the frames  $\mathbf{M}_j^{\text{fam}\alpha}$  and of the dispersion parameters  $\kappa_{\text{fam}\alpha}$  is expressed by first order rate equations

$$\begin{aligned} \dot{\mathbf{M}}_j^{\text{fam}\alpha} &= \boldsymbol{\omega}_{\text{fam}\alpha} \times \mathbf{M}_j^{\text{fam}\alpha} \quad \text{with } \boldsymbol{\omega}_{\text{fam}\alpha} = \frac{\omega_{\text{tar}\alpha}}{t_\omega^*} \mathbf{N}_\omega^{\text{tar}\alpha} \\ \dot{\kappa}_{\text{fam}\alpha} &= \frac{1}{t_\kappa^*} (\kappa_{\text{tar}\alpha} - \kappa_{\text{fam}\alpha}) \quad \text{with } \kappa_{\text{tar}\alpha} = \Gamma/2, \end{aligned} \quad (5)$$

where  $\boldsymbol{\omega}_{\text{tar}\alpha} = \omega_{\text{tar}\alpha} \mathbf{N}_\omega^{\text{tar}\alpha}$  is the Rodrigues rotation vector of the rotation tensor  $\mathbf{R}^{\text{tar}\alpha} = \mathbf{M}_j^{\text{tar}\alpha} \otimes \mathbf{M}_j^{\text{fam}\alpha}$ . In (5)  $t_\omega^*$  and  $t_\kappa^*$  can be interpreted as time relaxation parameters of the reorientation process. The remodeling process is introduced into an incompressible finite shell formulation [10], where the incompressibility constraint is enforced through elimination of displacement and strain variables.

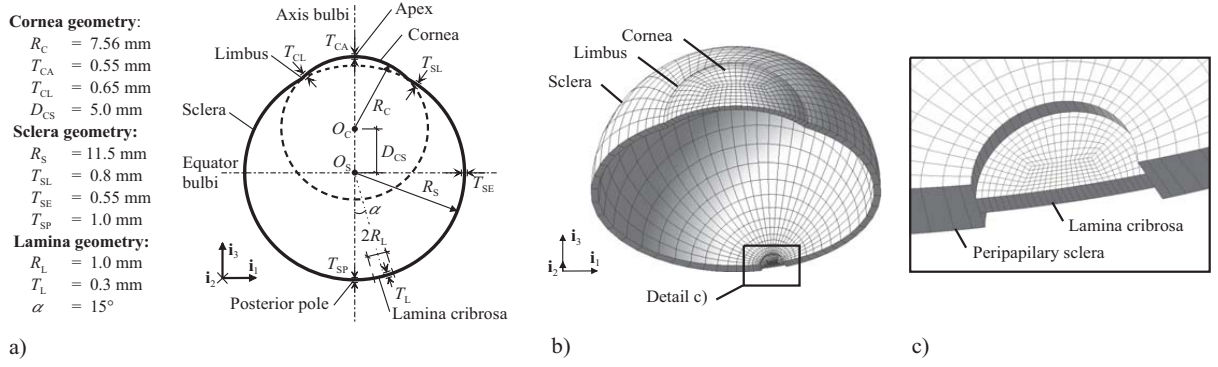


Figure 3: Numerical human eye model. (a) Geometry. (b) Finite element discretization. (c) Detail view of the peripapillary sclera and lamina cribrosa finite element discretization.

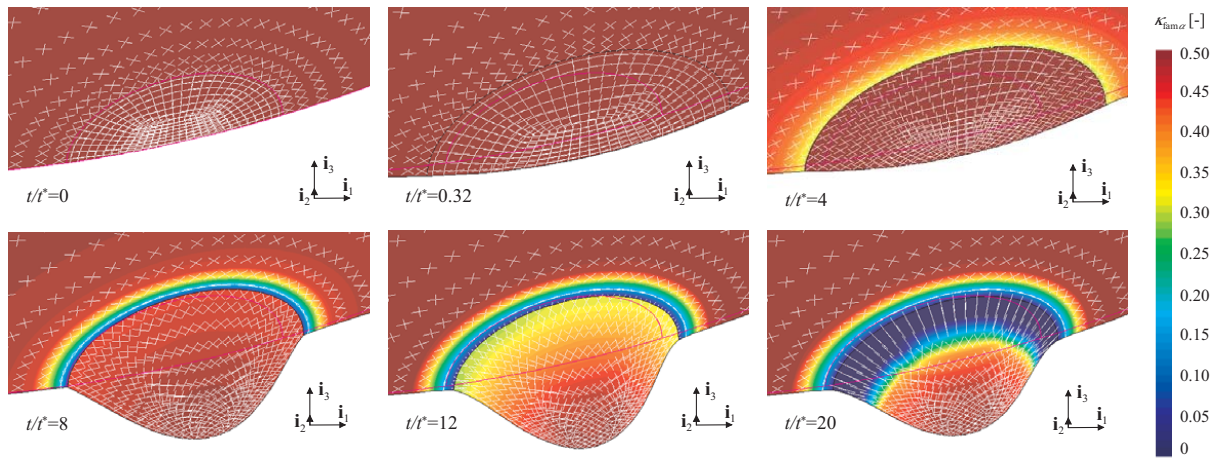


Figure 4: Snapshots of the remodeling process of the deformed mid-surface of the peripapillary sclera and lamina cribrosa at different points in normalized time  $t/t^*$  (deformations 10-fold magnified). Contour plot: the dispersion parameters  $\kappa_{fam\alpha}$  representing randomly distributed fibrils for  $\kappa_{fam\alpha} = 0.5$  and perfectly aligned fibrils for  $\kappa_{fam\alpha} = 0$ . White lines: the mean fibril orientations  $M_1^{fam\alpha}$  of the two fibril families ( $fam\alpha = 1, 2$ ).

The remodeling algorithm has been applied to numerical human eye model (Figure 3), where the initial constitutive parameters have been identified from the inflation experiments. Selected snapshots of the remodeling process towards a homeostatic state are presented in Figure 4. Normalized time steps are held fixed  $\Delta t/t^*$  throughout the analysis, where the time relaxation parameter  $t^*$  accounts for the speed of the microstructural adaptation. The remodeling process is characterized by three evolution periods. In the first period ( $0 \leq t/t^* \leq 0.32$ ) the intraocular pressure is increased incrementally to the physiological value  $p_{IOP} = 16$  mmHg. In this loading period the optic nerve head is mainly subjected to membrane deformations. Then, the pressure is held constant while the collagen network is allowed to remodel until a homeostatic state occurs. In the second evolution period ( $0.32 < t/t^* \lesssim 10$ ) the scleral canal expansion is significantly reduced due to the development of a fibrillar ring surrounding scleral canal. As this ring of fibrils is formed the stress environment of the lamina gradually changes from a membrane to a bending dominated state (see the increased cupping of the lamina from  $t/t^* = 4$  to  $t/t^* = 8$  in Figure 4). The bending of the lamina cribrosa is accompanied by high transversal shear stresses at the periphery of the lamina characterizing the third evolution period ( $10 \lesssim t/t^* \leq 20$ ). In this evolution period lamina fibrils tend to rotate out of the shell surface with a preferred radial orientation at the periphery to increase shear resistance, which in turn

reduces the lamina cupping slightly.

#### 4 COMPUTATIONAL MULTISCALE MODELING OF THE LAMINA CRIBROSA

To gain insight into the multi-scale phenomena related to axoplasmatic flow blockage in glaucoma a numerically coupled two-scale analysis (Figure 5a) is performed investigating the relationship between the intraocular pressure at the macro-level and the stress environment of the nerve fiber bundles at the meso-level of the lamina cribrosa. The extracellular matrix in the lamina forms a multilayered sieve-like meso-structure with several holes leaving enough space for axon bundles passing through [15]. A representative volume element with periodic boundary condition is used to model the biomechanical response of the sieve-like meso-structure of the lamina cribrosa. The two-scale model is characterized by preferred material directions following curvilinear paths at the macro-scale. To assure consistent meso-macro transitions of tensor variables the derivation of the generalized homogenization scheme [3, 16, 17] is based on different physical spaces at different scales.

According to Figure 5b the absolute peak value of the maximal principal stress within the nerve bundles of all representative volume elements is increasing until a physiological intraocular pressure level ( $\approx 16$  mmHG) has been reached and remains almost constant for elevated pressure levels. In contrast, the peak value of the in-plane shear stress in nerve bundles is continuously increasing for increasing pressure levels, which might indicate an increasing susceptibility to axonal transport blockage. From long term medical observations of patients suffering from glaucoma it is known that visual defects occur initially at outer region of the visual field. The related ganglion cell axons are leaving the optic nerve head at the periphery of the lamina cribrosa. Exactly this region has been identified by the numerical two-scale model to have the highest values of in-plane shear stress in nerve bundles (Figure 5c).

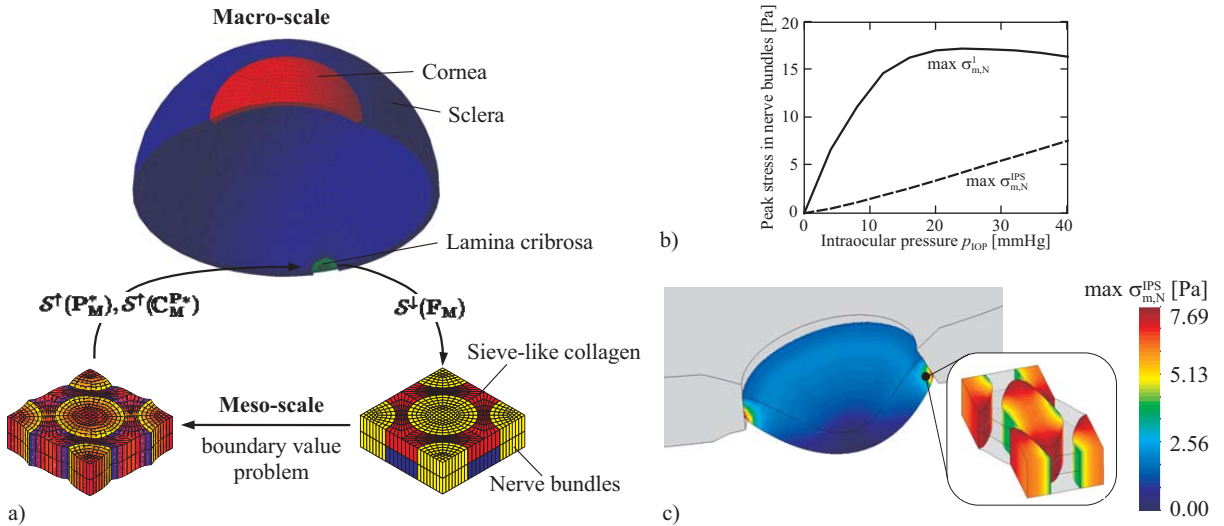


Figure 5: (a) Numerical two-scale analysis of the human eye based on the generalized computational homogenization scheme [3]. (b) Peak values of the maximal principal Cauchy stress  $\max \sigma_{m,N}^1$  and the in-plane shear stress  $\sigma_{m,N}^{IPS}$  of within the nerve bundles at the micro-scale for varying levels of intraocular pressure at the macro-scale. (c) Contour plot of  $\sigma_{m,N}^{IPS}$  at elevated intraocular pressure  $p_{IOP} = 40$  mmHg.

## 5 CONCLUDING REMARKS

The numerical findings presented here are substantial for the development of realistic models of the optic nerve head in the context of the ocular disease glaucoma. The remodeling analysis has demonstrated the strong influence of the collagen network morphology existing in the peripapillary sclera on the stress environment of the lamina. Accordingly, the mechanical properties of the peripapillary sclera might play a significant role in the development of glaucoma. The numerical remodeling algorithm presented a novel, biomechanical explanation of the spatial orientation of fibrillar collagen in the optic nerve head. The peripapillary ring of fibrils significantly shielded axons in the lamina from intraocular pressure related membrane deformations and high tensile stresses, while the radial oriented fibrils in the lamina periphery reinforced the lamina against bending deformations. Both predicted morphologies are in good agreement with experimental observations [15, 18–21] and might be essential to provide a secure passage for optic nerve axons exiting the eye shell at the optic nerve head.

The numerical two-scale analysis indicated that the microarchitecture of the lamina cribrosa is capable to effectively protect the embedded nerve bundles from high tensile stresses at elevated intraocular pressure levels, but not from in-plane shear stresses which might increase the susceptibility to axonal transport blockage known in glaucoma.

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