Continuum mechanics and computational modeling of ocular tissues for in silico therapies

E. Friedmann, A. Drobny

Institute of Mathematics, University of Kassel, Germany
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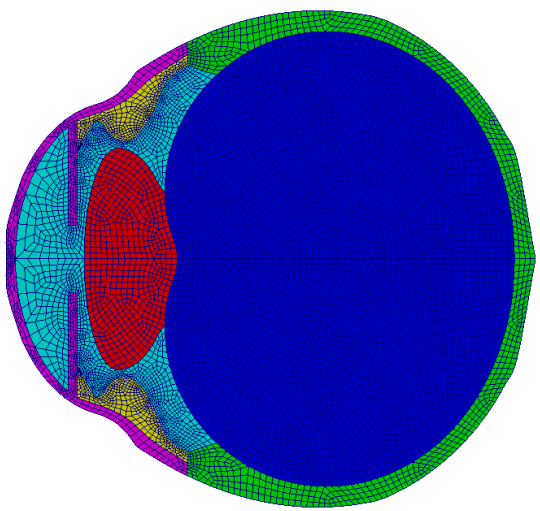

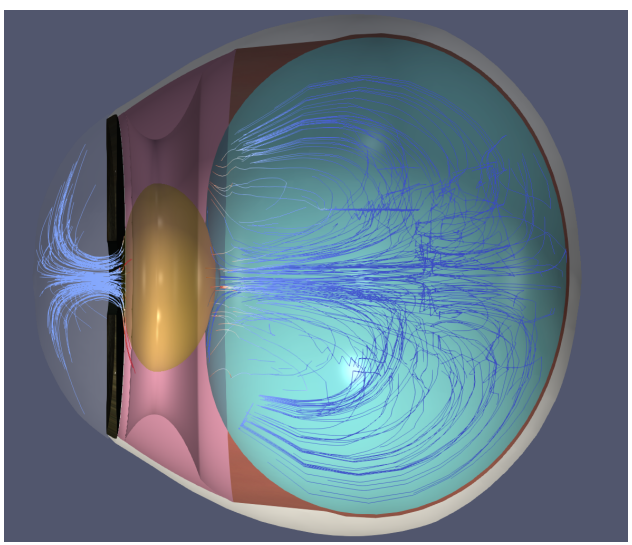

Overview

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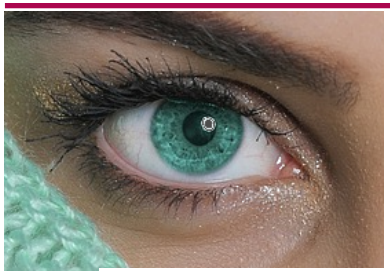
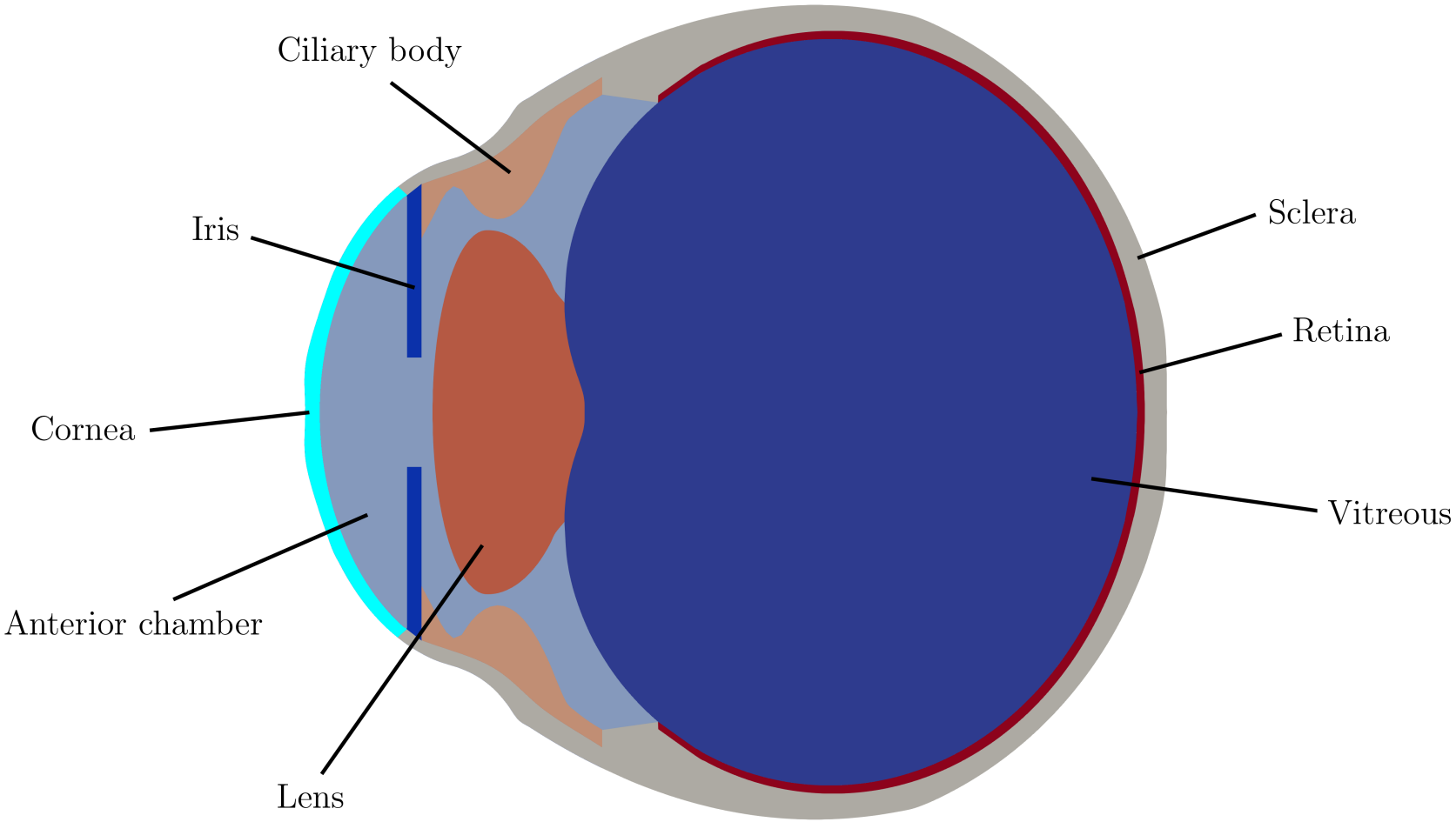
- Geometry: The Virtual Human Eye
- A living system: modeling the physiology (flow and structures)
- The pathophysiology (glaucoma, Age-related Macular Degeneration, AMD)
- Modeling & Simulation of the treatment (stent, trabeculectomy, pharmacological models)
- Analyzing the treatment efficacy

Anatomy of the eye

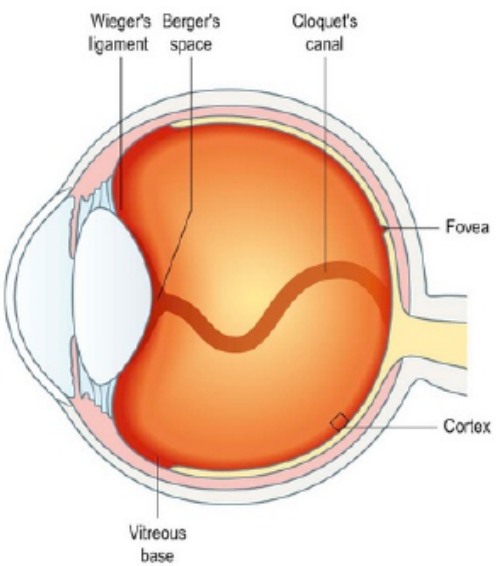


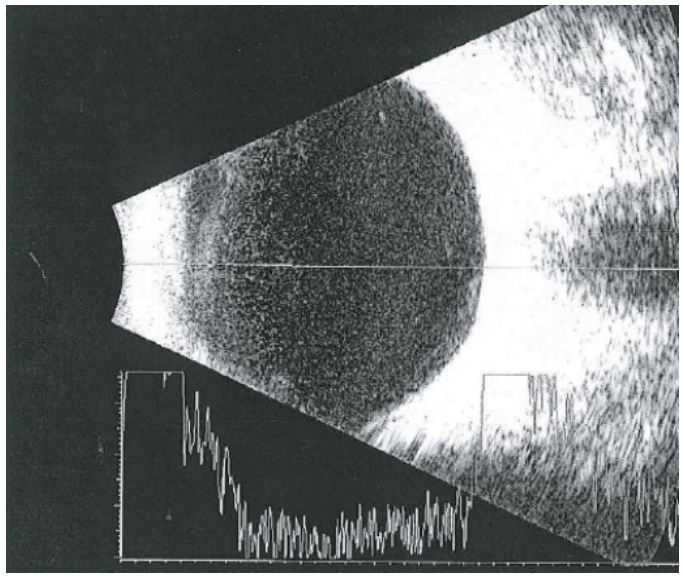


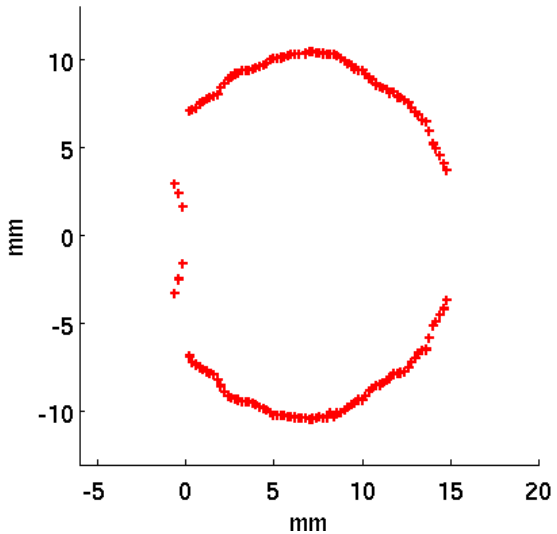
Geometrical model of the Eye

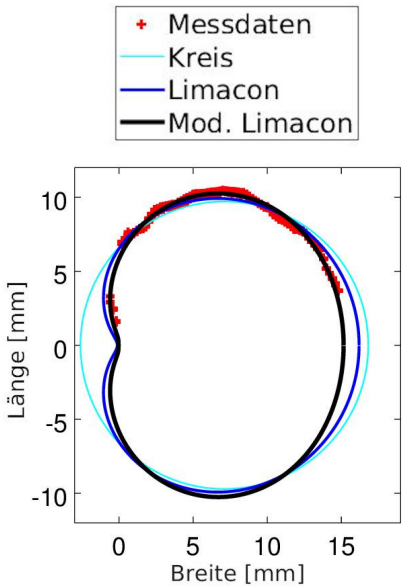
- each component of the eye is represented by a suitable mathematical function
- the parameters of the functions are fitted to data
- data from imaging techniques: US, MRI, OCT

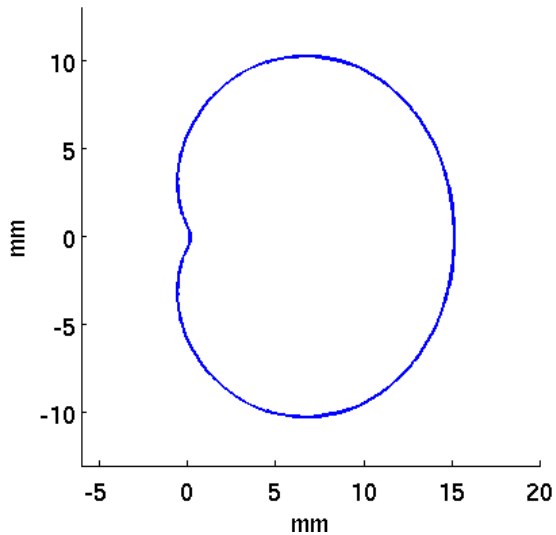
A model for the vitreus

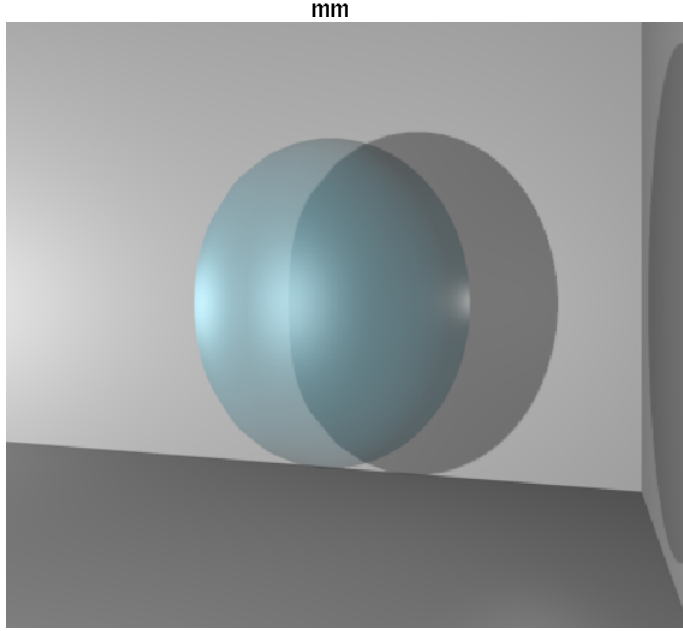












$$X = R(\phi)\cos(\phi),\ Y = R(\phi)\sin(\phi)\cos(\varphi),\ Z = R(\phi)\sin(\phi)\sin(\varphi),\ R(\phi) = p_1 + p_2\cos(\phi) + p_3\cos(\phi)^3$$

A model for the lens

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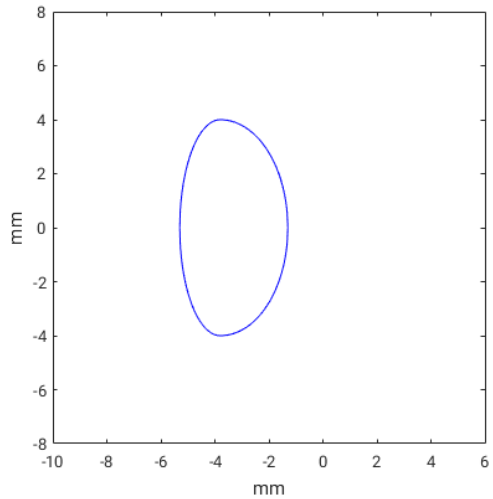
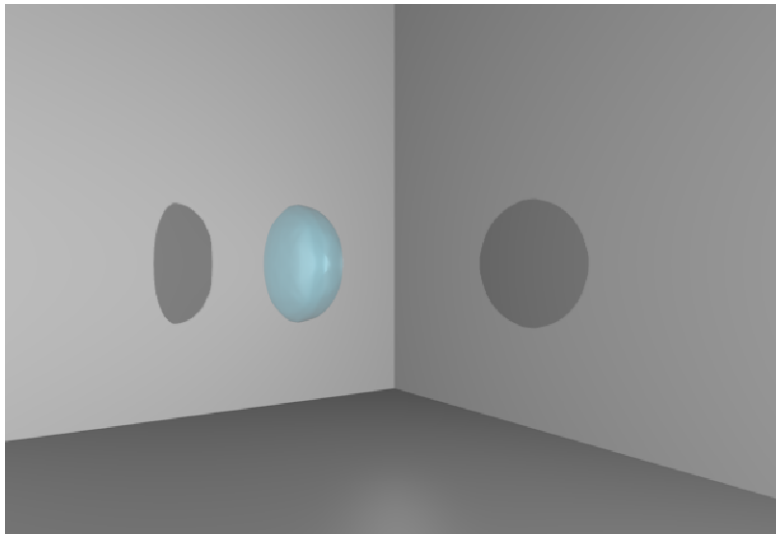
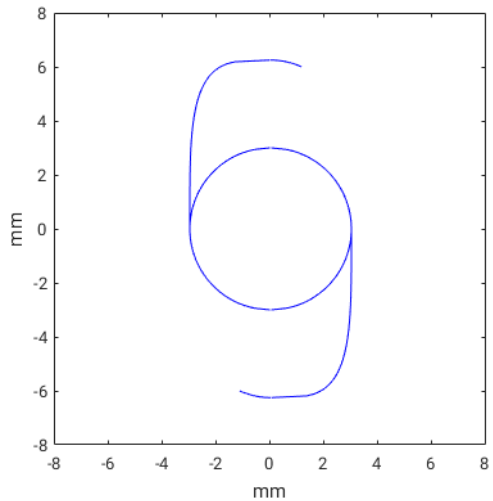
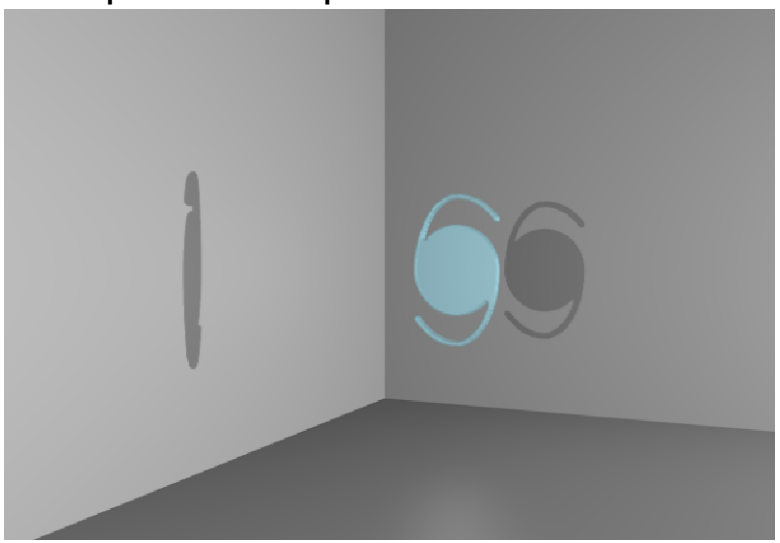
natural lense: 2 hemiellipsoids





artificial lense: thin cylinder & haptics: 2 ellipsoid-sections





A model for the iris

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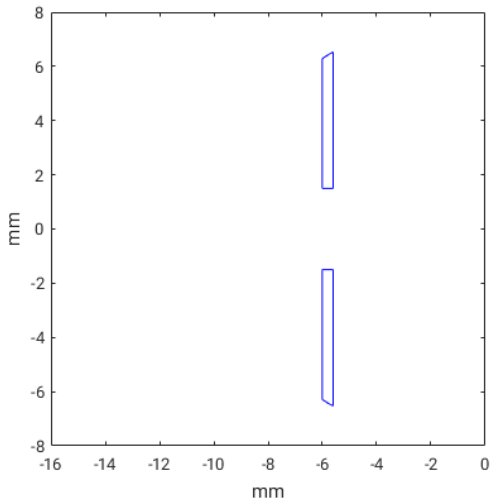
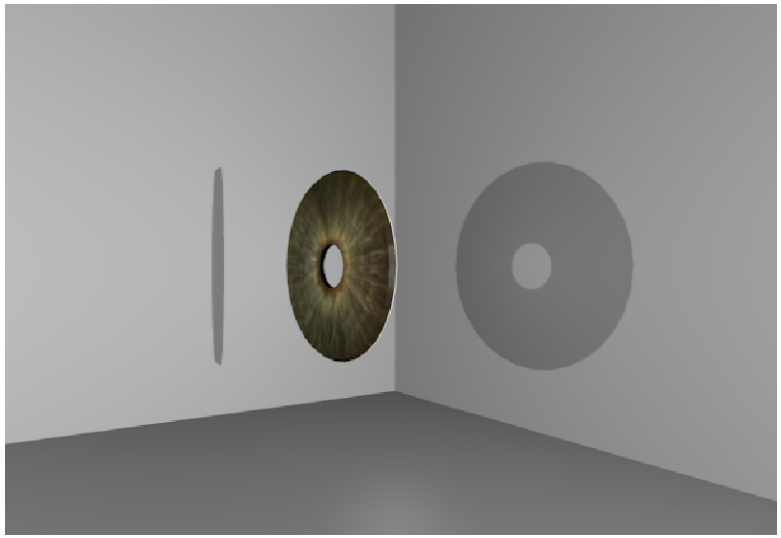
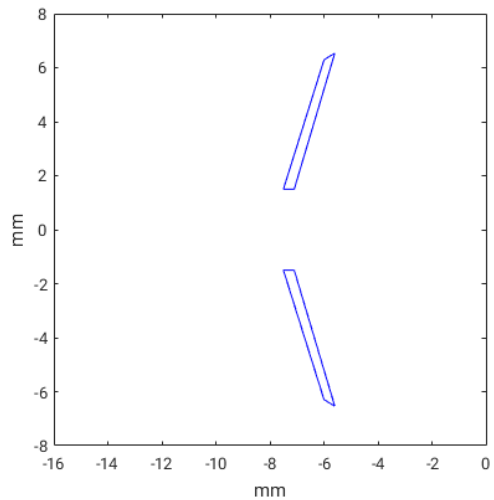
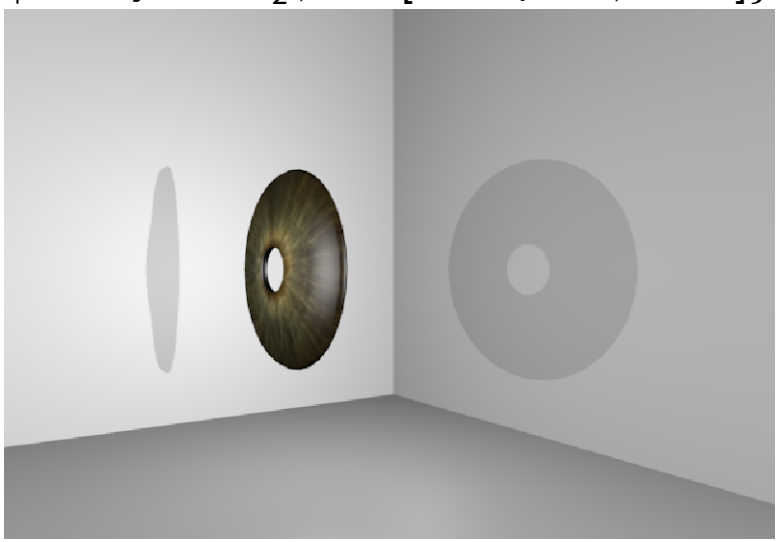
healthy iris $I := \{x, y, z \in \text{hemiellipsoid} | z^2 + y^2 > R^2, x \in [a, b]\}$



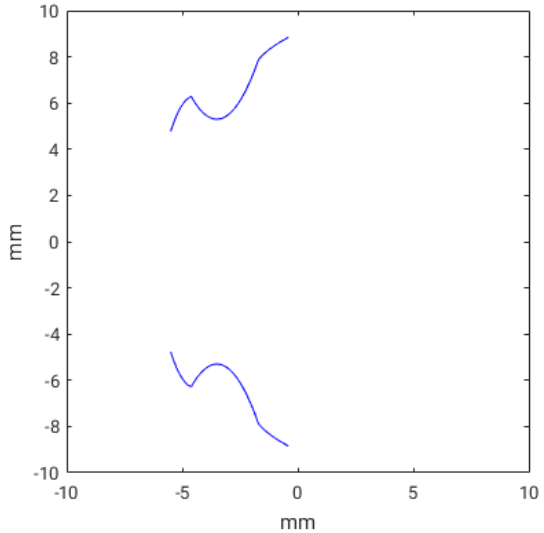


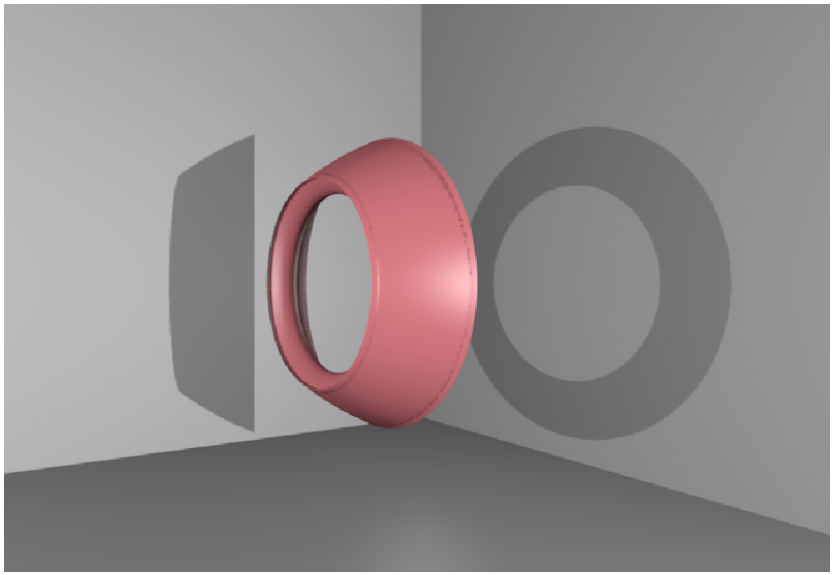
pathological iris $I := M \backslash \{x, y, z \in \mathbb{R} \,|\, z^2 + y^2 = R_z^2, x \in [h - a_I + s, h + s]\}$





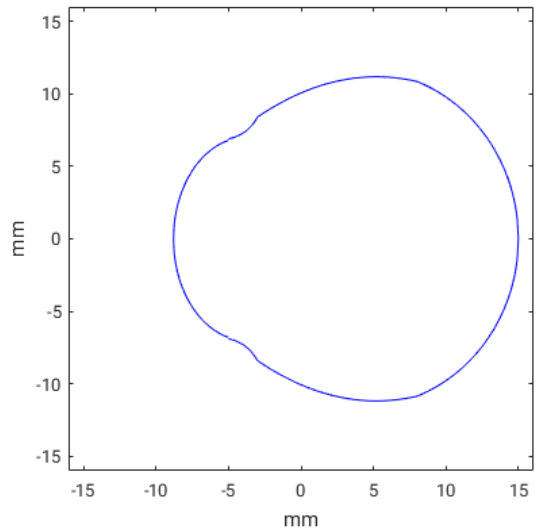
A model for the ciliary body

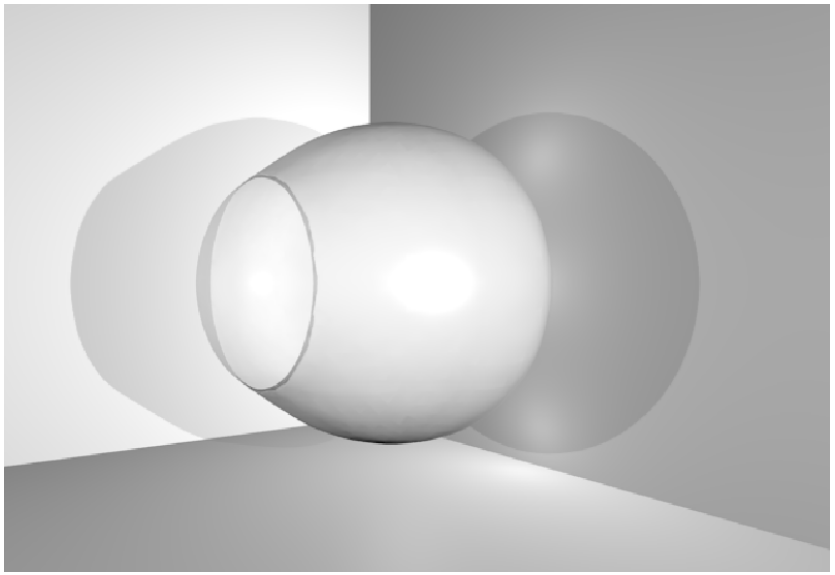




$$cb(x) = \begin{cases} a_1(x+4.5)^2 + a_2 & \text{for } -5.5 \leq x \leq -4.6 \\ a_3(x+3.5)^2 + a_4 & \text{for } -4.61 \leq x \leq -1.7 \\ a_5 \exp x + a_6 & \text{for } -1.7 \leq x \leq 3.66 \end{cases}$$

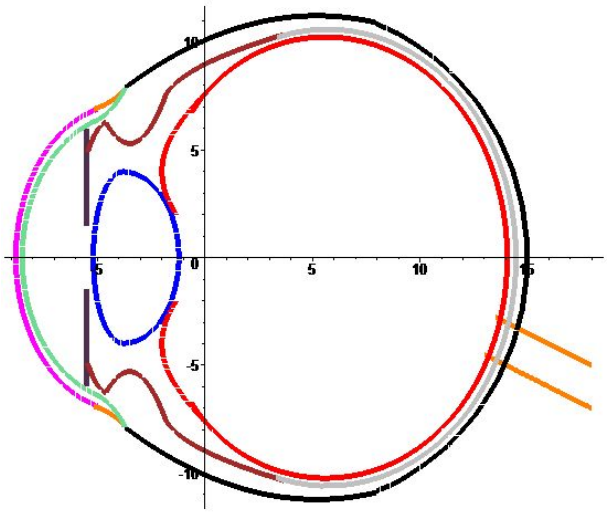
A model for the cornea & sclera

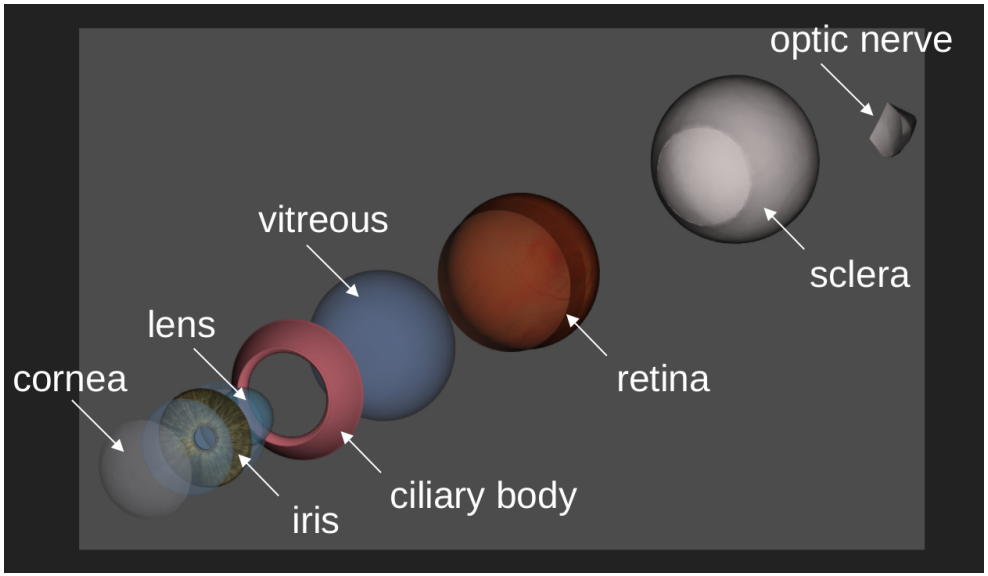


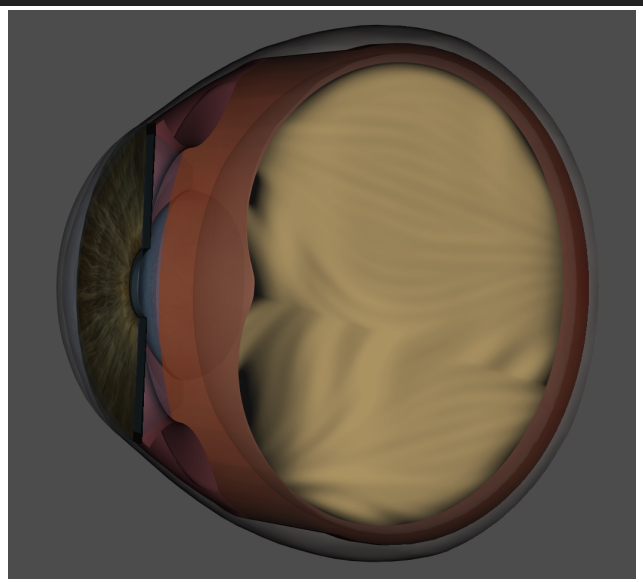


$$eye(x) = \begin{cases} \sqrt{bb^2 - \left(\frac{(x-4.2)\cdot bb}{aa}\right)^2} & \text{for } 8 \le x \le 15 \\ c_1(x-5.2)^2 + c_2 & \text{for } -3 \le x \le 8 \\ c_3 \exp x + c_4 & \text{for } -5 \le x \le -3 \\ \sqrt{b^2 - \left(\frac{(x-4.2)\cdot b}{a}\right)^2} & \text{for } -8.8 \le x < -5 \end{cases}$$

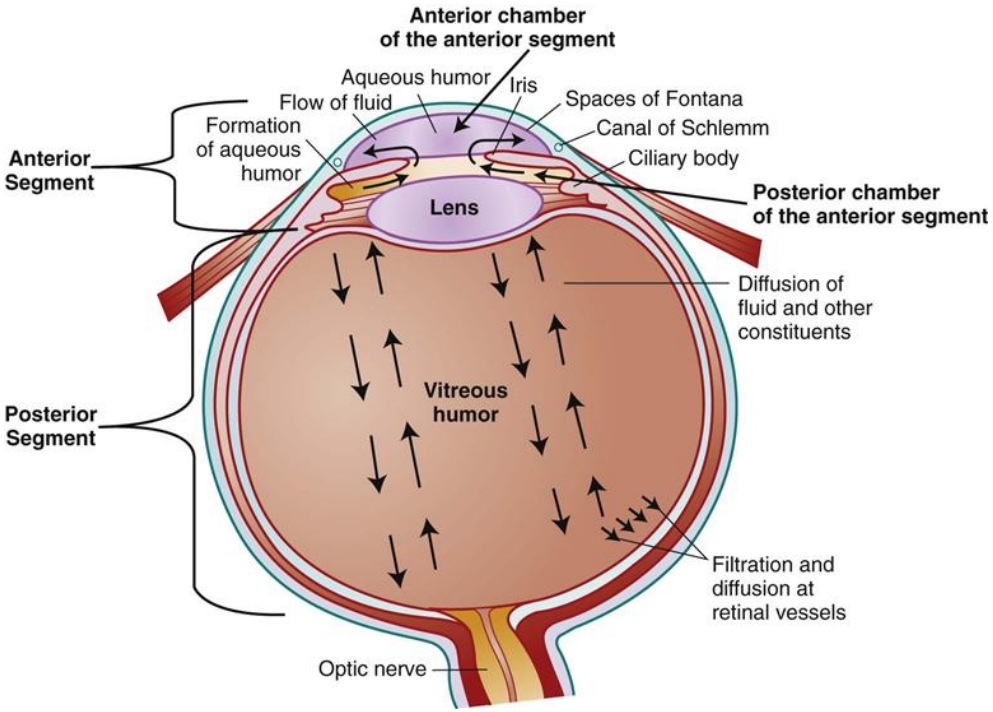
The Virtual Eye







Physiology of the human eye



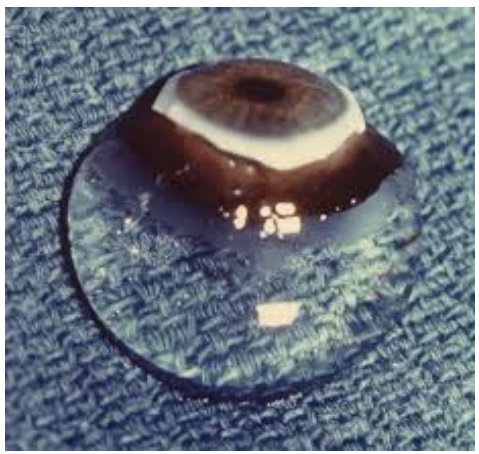


Fig. 48.2 www.nursekey.com/assessment-of-the-eye-and-vision-2, [Sebag, Springer, 2014]

- elastic structures: cornea, sclera, lens
- viscoelastic vitreous (healthy case)
- flow: aqueous humour is produced in the ciliary body, fills the anterior chamber and leaves through trabecular meshwork
- flow: small fraction flows through the vitreous
- chemistry (signaling)
- exchange of molecules (diffusion, convection)

Governing equations: elastic structures

cornea, sclera & lens

- Conservation of momentum in Lagrangian framework

$$\hat{\rho}_s^0 \partial_t^2 \hat{u}_s - \widehat{\mathrm{div}}(\hat{\Pi}) = \hat{\rho}_s^0 \hat{f}_s \quad \text{in } \hat{\Omega}_s, t \in I$$

with $\hat{\Pi} = \frac{\partial \hat{W}}{\partial \hat{F}}$, $\hat{J} = \det \hat{F}, \hat{F} := \hat{I} + \hat{\nabla} \hat{u}_s$, $\hat{C} = \hat{F}^T \hat{F}$ and a Neo-Hookean solid for cornea & sclera: [Simo et al. 1985, Grytz et al. 2014]

$$\hat{\Pi} = \mu \hat{J}^{-2/3} \left(\hat{F} - \frac{1}{3} \mathrm{tr}(\hat{C}) \hat{F}^{-T} \right) + \kappa \ln \hat{J} \hat{F}^{-T}$$

lens: [Wilde 2011]

$$\hat{\Pi} = \mu \hat{J}^{-2/3} \left(\hat{F} - \frac{1}{3} \mathrm{tr}(\hat{C}) \hat{F}^{-T} \right) + \kappa (\hat{J} - 1) \hat{J} \hat{F}^{-T}$$

- Mixed formulation

$$\begin{aligned} \hat{\rho}_s^0 \partial_t \hat{v}_s - \widehat{\mathrm{div}}(\hat{\Pi}) &= \hat{\rho}_s^0 \hat{f}_s \quad && \text{in } \hat{\Omega}_s, t \in I \\ \partial_t \hat{u}_s - \hat{v}_s &= 0 && \text{in } \hat{\Omega}_s, t \in I \end{aligned}$$

+ Initial and boundary conditions (Dirichlet and Neumann b.c.)

Anterior aqueous humor flow

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model equations:

- steady Stokes equations in the anterior chamber
- Darcy model for the flow through the trabecular meshwork (TMW)

Parameter:

- volume of the anterior chamber $V = 0.16$ ml
- gravitation $f = (-g, 0, 0)$
- viscosity of the aqueous humor $\nu = 7 \cdot 10^{-7}$ Pa·s
- inflow (production rate in the ciliary body) $v_{\text{in}} = 2$ mm^3/min
- permeability of the trabecular meshwork (TMW) $K = 0.778 \cdot 10^{-9}$ mm^2
- outflow condition at TMW: episcleral pressure 1200 Pa $= 9$ mmHg
- pupil aperture d $= 3$mm

Model of anterior aqueous humor flow

$$
\begin{aligned}
-\nabla \cdot \mathbb{T}(u,p) &= f \\
\nabla \cdot u &= 0 \\
u &= u_{\text{in}}^{CB} \text{ on } \Gamma_{\text{in}} \\
u &= 0 \text{ on } \Gamma_{\text{ns}} \\
n \cdot \mathbb{T}(u,p) \cdot n &= p_0 \text{ on } \Gamma_{\text{out}} \\
n \cdot \mathbb{T}(u,p) \cdot \tau &= \tilde{\alpha} u \cdot \tau \text{ on } \Gamma_{\text{out}},
\end{aligned}
$$

with $\mathbb{T}(u,p) = 2\nu\mathbb{D}(u) - pI$, the normal vectors n, the tangential vectors τ, $p_0 = \frac{1}{|\Omega_p|}\int_{\Omega_p} p(x)\,dx$ the pressure of the TM calculated via Darcy and $\tilde{\alpha}$ donates the friction constant

$$
\begin{aligned}
-\nabla \cdot (\frac{K}{\nu}\nabla p) &= f_2 \\
\frac{K}{\nu}\nabla p \cdot n &= 0 \text{ on } \Gamma_{\text{wall}} \\
\frac{K}{\nu}\nabla p \cdot n &= u_{\text{in}}^{TW} \cdot n \text{ on } \Gamma_{\text{in}} \\
p &= p_{\text{out}} \text{ on } \Gamma_{\text{out}},
\end{aligned}
$$

Simulations for the aqueous humor flow

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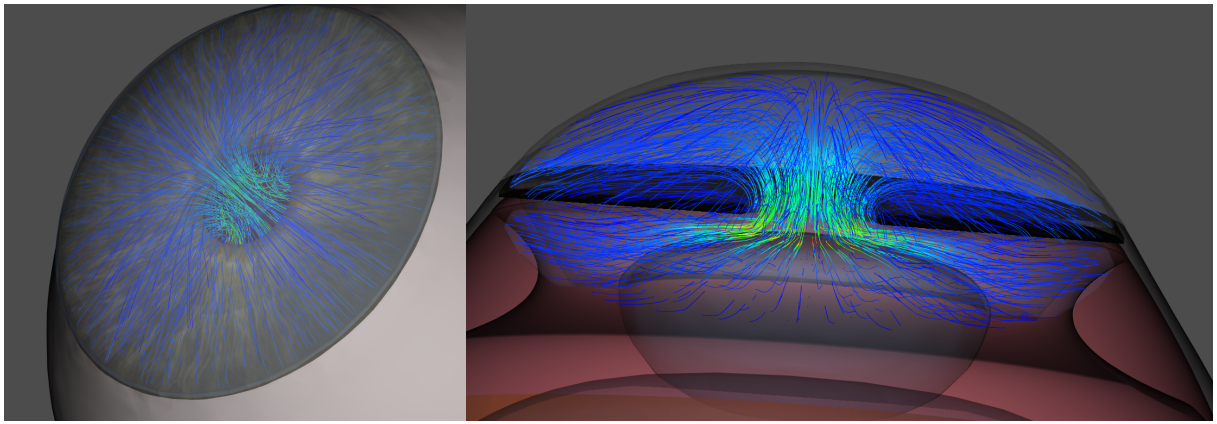
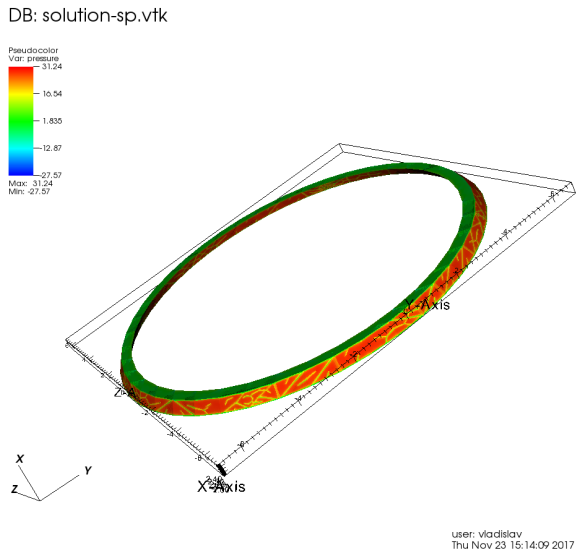
Stokes model: Taylor Hood Finite Elements



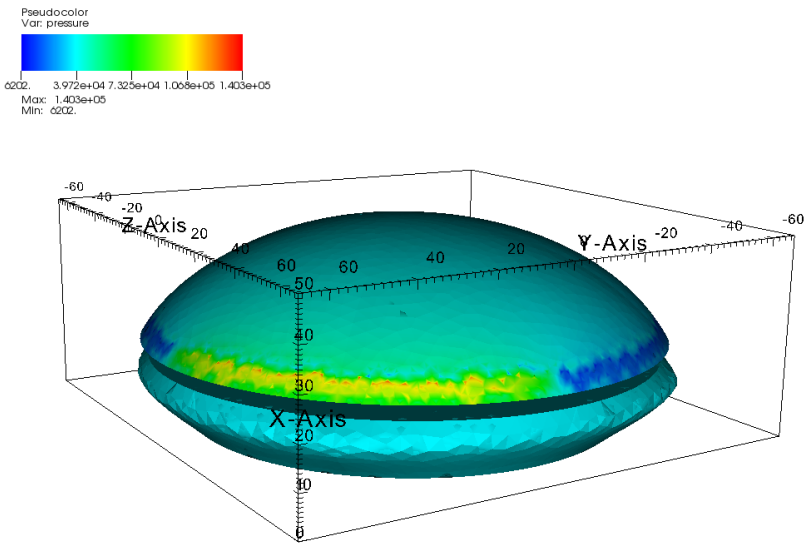
streamlines for the aqueous humor flow

Darcy model: Lagrange Finite Elements

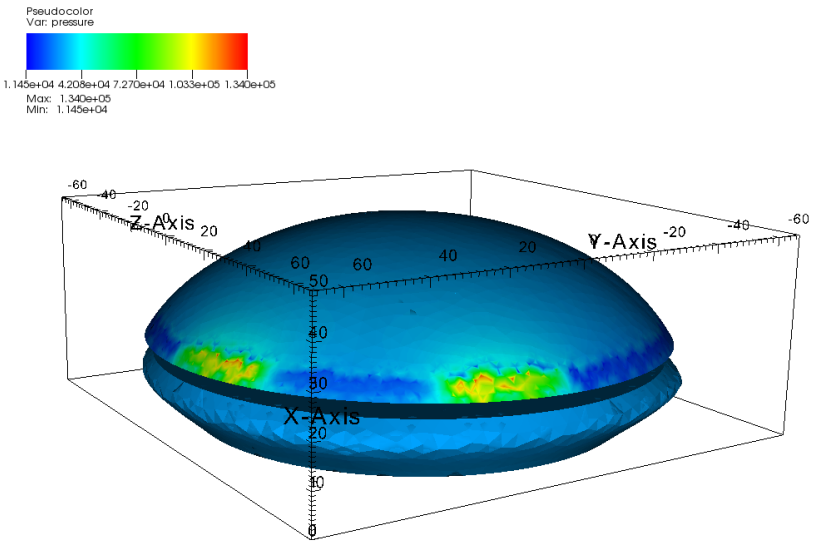


trabecular meshwork

Pathophysiology: glaucoma

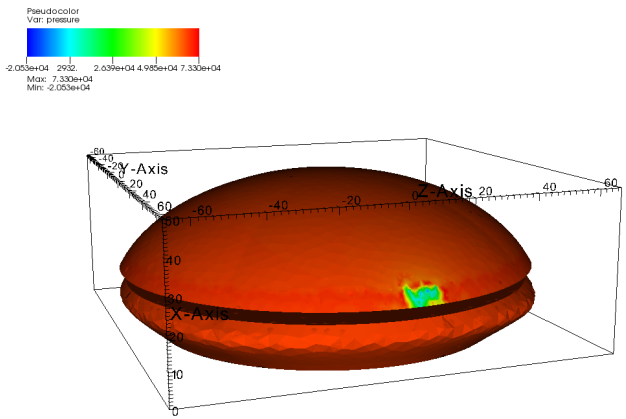


IOP=28.37 mmHg partly clogged TMW

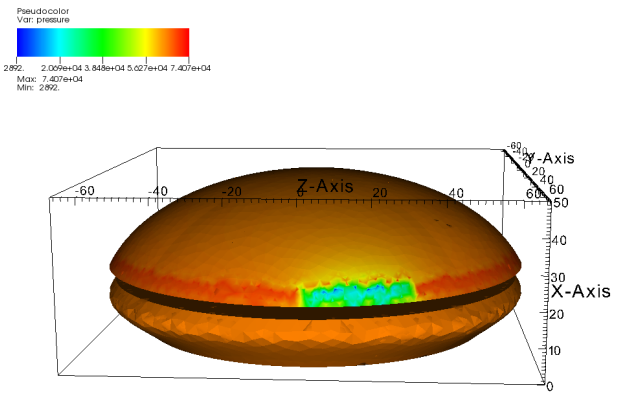


IOP=23.17 mmHg (−18%) after intervention (trabeculectomy)

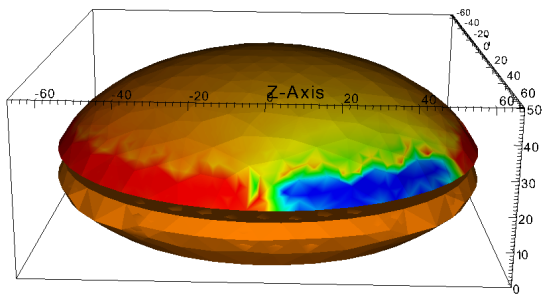
Pathophysiology: glaucoma



IOP drops from 51.1 to 50.15 mmHg with a 1 mm stent



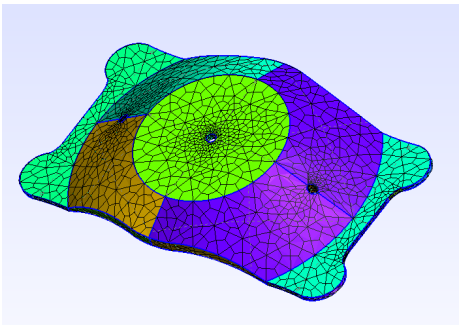
IOP drops from 51.1 to 48.52 mmHg with a 3 mm cut



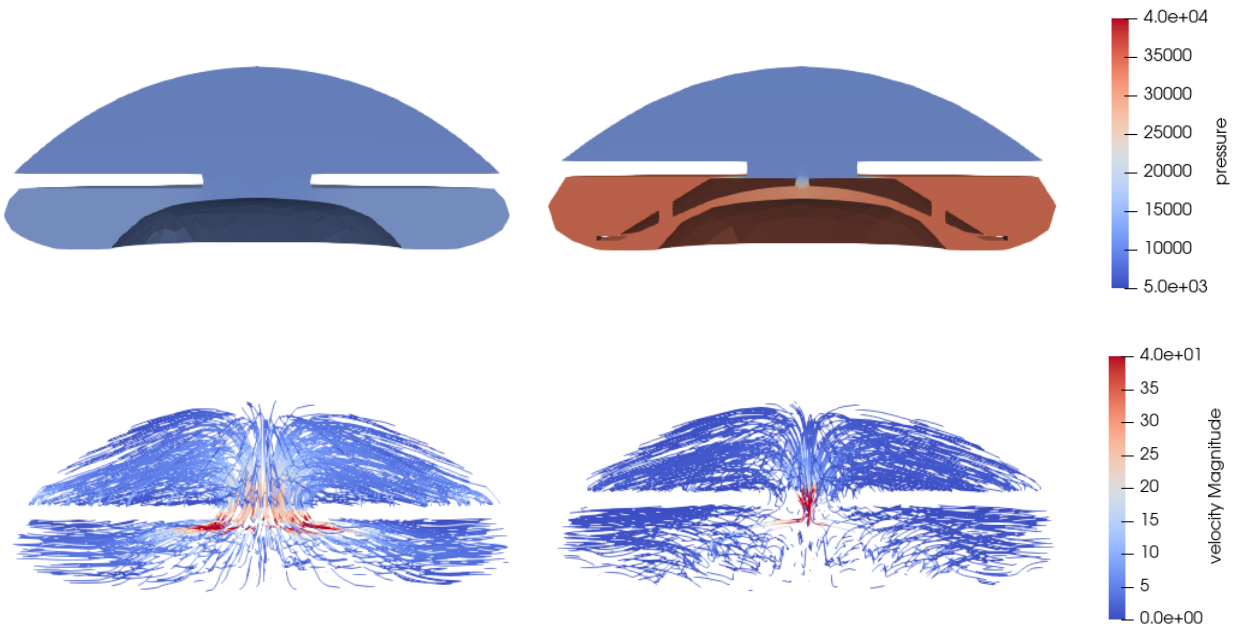
IOP=44 mmHg (-12%) with a 6 mm cut

Refractive surgery

$d = 360\ \mu$m, vaulting $v = 350\ \mu$m, $K = 0.778 \cdot 10^{-9}$ mm^2, $\nu = 7 \cdot 10^{-7}$ Pa·s



IOP: 10.09 mmHg for the healthy eye
IOP: 17.50 mmHg for the eye with pIOL.



Posterior aqueous humor flow

- general balance equations:

$$\begin{aligned} \rho_f \partial_t v_f + \rho_f (v_f \cdot \nabla) v_f - \mathrm{div}\,\mathbb{T} &= \rho_f f \quad && \text{in } \Omega_f, t \in I \\ \mathrm{div}\, v_f &= 0 \quad && \text{in } \Omega_f, t \in I \end{aligned}$$

  - pathological (liquified) vitreous: Navier-Stokes

$$\mathbb{T} = -p_f I + 2\rho_f \nu_f D(v_f), \quad D(v_f) := \frac{1}{2}(\nabla v_f + \nabla v_f^T)$$

Posterior aqueous humor flow

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$$\mathrm{div} v_f = 0 \quad \text{in } \Omega_f, t \in I$$

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  - healthy vitreous: viscoelastic Burgers-type model [Tůma, Stein, Prusa, EF 2018], [Tram & Swindle-Reilly, 2018], [Sharif-Kashani et al. 2011]

$$\mathbb{T} = -p_f I + 2\rho_f \nu_f D(v_f) + \mu_1 (B_1 - I) + \mu_2 (B_2 - I) \text{ with}$$

$$\overset{\triangledown}{B}_1 + \frac{\mu_1}{\nu_1}(B_1 - I) = 0, \quad \overset{\triangledown}{B}_2 + \frac{\mu_2}{\nu_2}(B_2 - I) = 0 \text{ and}$$

$$\overset{\triangledown}{B}_1 := \partial_t B_1 + (v_f \cdot \nabla) B_1 - (\nabla v_f) B_1 - B_1 (\nabla v_f)^T$$

- boundary conditions: parabolic inflow + no-slip condition at the lens
  + outflow: $\mathbb{T} n \cdot n = k_{\text{perm}} v \cdot n$, $\mathbb{T} n \cdot \tau = 0$

Disease & Treatment

Disease: Age-related macular degeneration (AMD)

- results in vision loss due to abnormal blood vessel growth underneath the retina
- leading cause of irreversible blindness among the older generation
- affected around 6.2 million people globally (status 2015)
- the age-related changes that stimulate the pathology are incompletely understood
- measure of the severity of the disease: vascular endothelial growth factor (VEGF)

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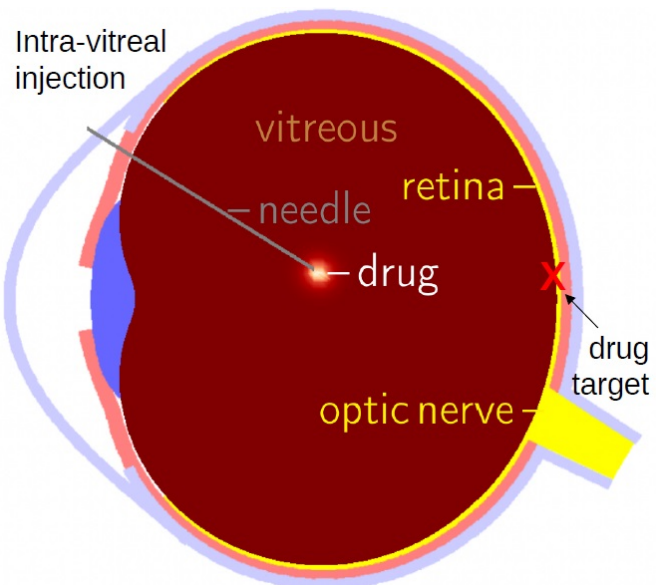


Treatment: Anti-VEGF intravitreal injections

- 0.05ml Eylea (Aflibercept) or Lucentis (Ranibizumab) every month at the beginning
- drug diffuses to the retina and effects there locally at the macula

Governing equations for molecules exchange

- Convection-diffusion equation

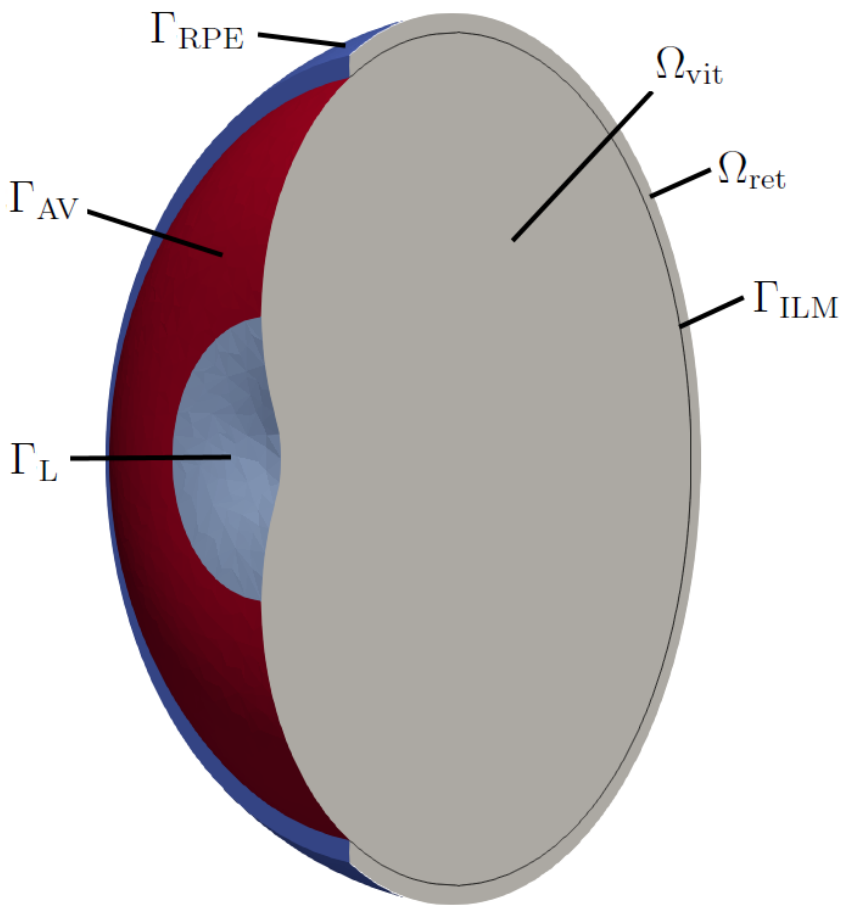
$$\partial_t c + (v \cdot \nabla)c - D\Delta c = 0 \text{ in } \Omega_f, t \in I$$

- Underlying flow: Burgers-type or Navier-Stokes
- Boundary conditions:

$$\begin{aligned} -(D\nabla c) \cdot n &= 0 && \text{on } \Gamma_{\text{lens}} \\ -(D\nabla c) \cdot n + c(v \cdot n) &= p_0 c && \text{on } \Gamma_{\text{hyaloid}} \\ -(D\nabla c) \cdot n + c(v \cdot n) &= p_1 c && \text{on } \Gamma_{\text{retina}} \end{aligned}$$

- $+$ initial conditions

Drug therapy in the vitreous & retina



Sketch of the two domains sliced in the middle

- Vitreous: System of convection-diffusion-reaction equations
- Retina: System of diffusion-reaction equations
- Reaction chain:

  [Hutton-Smith et al. 2018]

$$\mathrm{A} + \mathrm{V} \underset{k_{\mathrm{off}}}{\overset{2k_{\mathrm{on}}}{\rightleftharpoons}} \mathrm{VA}$$

$$\mathrm{A} + \mathrm{VA} \underset{2k_{\mathrm{off}}}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}} \mathrm{AVA}$$

- Drug: A, VEGF: V, drug-VEGF complex VA, drug-VEGF-drug complex AVA

Pharmacological model in the vitreous Ω_v

- convection-diffusion equation + binding & dissociation mechanism

$$\frac{\mathrm{d}c_{a_{vit}}}{\mathrm{d}t} + v_v \cdot \nabla c_{a_{vit}} - D_{a_{vit}} \Delta c_{a_{vit}} = (k_{off} c_{va_{vit}} - 2k_{on} c_{v_{vit}} c_{a_{vit}}) + (2k_{off} c_{ava_{vit}} - k_{on} c_{a_{vit}} c_{va_{vit}}) \quad \text{in } \Omega_v, t \in I$$

$$\frac{\mathrm{d}c_{v_{vit}}}{\mathrm{d}t} + v_v \cdot \nabla c_{v_{vit}} - D_{v_{vit}} \Delta c_{v_{vit}} = (k_{off} c_{va_{vit}} - 2k_{on} c_{v_{vit}} c_{a_{vit}}) \quad \text{in } \Omega_v, t \in I$$

$$\frac{\mathrm{d}c_{va_{vit}}}{\mathrm{d}t} + v_v \cdot \nabla c_{va_{vit}} - D_{va_{vit}} \Delta c_{va_{vit}} = -(k_{off} c_{va_{vit}} - 2k_{on} c_{v_{vit}} c_{a_{vit}}) + (2k_{off} c_{ava_{vit}} - k_{on} c_{a_{vit}} c_{va_{vit}}) \quad \text{in } \Omega_v, t \in I$$

$$\frac{\mathrm{d}c_{ava_{vit}}}{\mathrm{d}t} + v_v \cdot \nabla c_{ava_{vit}} - D_{ava_{vit}} \Delta c_{ava_{vit}} = -(2k_{off} c_{ava_{vit}} - k_{on} c_{a_{vit}} c_{va_{vit}}) \quad \text{in } \Omega_v, t \in I.$$

Pharmacological model in the retina Ω_{ret}

- diffusion equation + binding & dissociation mechanism + VEGF production

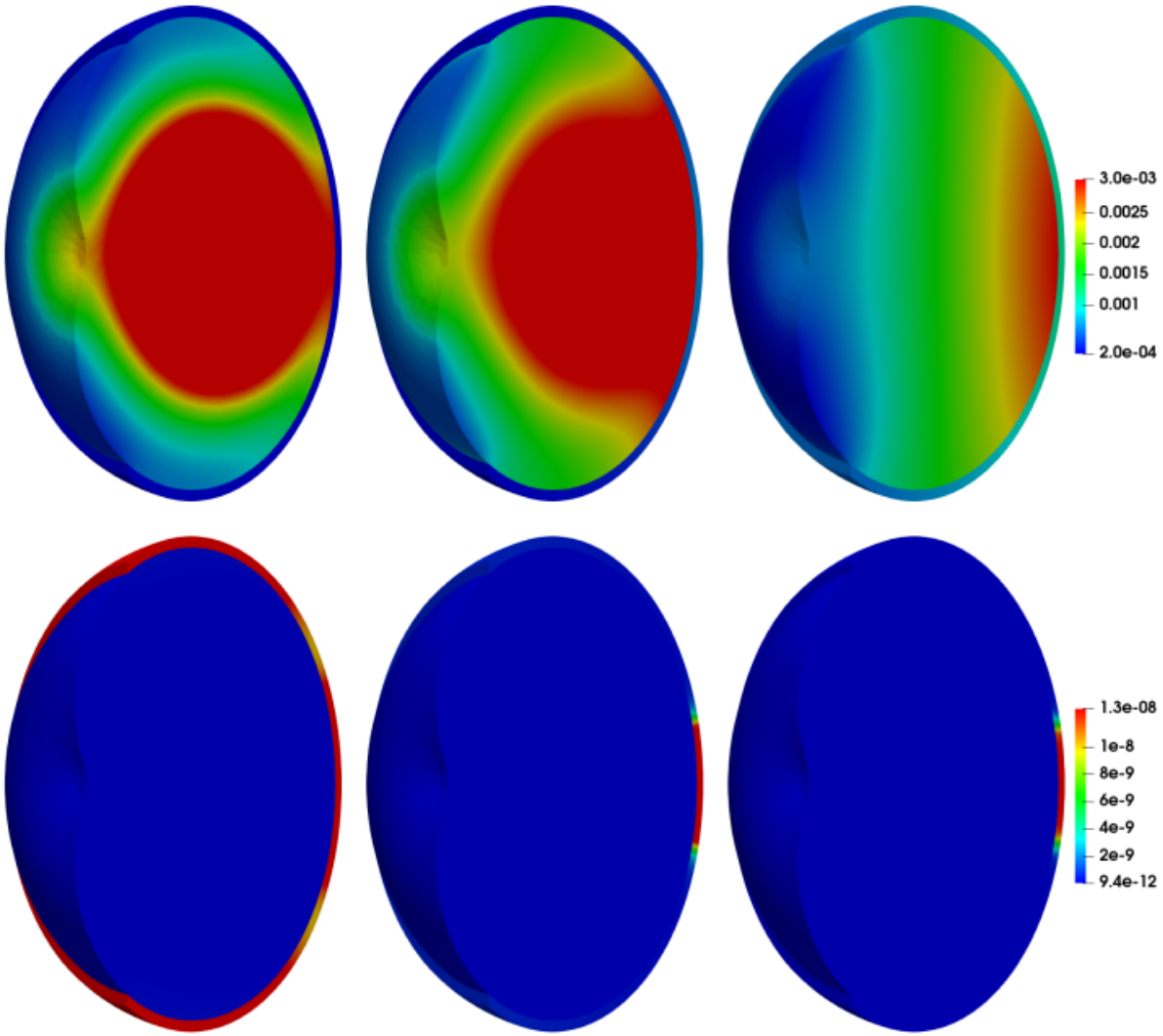
$$
\begin{aligned}
\frac{\mathrm{d}c_{\mathrm{a}_{\text{ret}}}}{\mathrm{d}t} - D_{\mathrm{a}_{\text{ret}}}\Delta c_{\mathrm{a}_{\text{ret}}} &= (k_{\text{off}}c_{\mathrm{va}_{\text{ret}}} - 2k_{\text{on}}c_{\mathrm{v}_{\text{ret}}}c_{\mathrm{a}_{\text{ret}}}) \\
&\quad + (2k_{\text{off}}c_{\mathrm{ava}_{\text{ret}}} - k_{\text{on}}c_{\mathrm{a}_{\text{ret}}}c_{\mathrm{va}_{\text{ret}}}) \qquad \text{in } \Omega_{\text{ret}}, t \in I \\
\frac{\mathrm{d}c_{\mathrm{v}_{\text{ret}}}}{\mathrm{d}t} - D_{\mathrm{v}_{\text{ret}}}\Delta c_{\mathrm{v}_{\text{ret}}} &= (k_{\text{off}}c_{\mathrm{va}_{\text{ret}}} - 2k_{\text{on}}c_{\mathrm{v}_{\text{ret}}}c_{\mathrm{a}_{\text{ret}}}) + \frac{k_{\text{p}}}{V_{\text{ret}}} \qquad \text{in } \Omega_{\text{ret}}, t \in I \\
\frac{\mathrm{d}c_{\mathrm{va}_{\text{ret}}}}{\mathrm{d}t} - D_{\mathrm{va}_{\text{ret}}}\Delta c_{\mathrm{va}_{\text{ret}}} &= -(k_{\text{off}}c_{\mathrm{va}_{\text{ret}}} - 2k_{\text{on}}c_{\mathrm{v}_{\text{ret}}}c_{\mathrm{a}_{\text{ret}}}) \\
&\quad + (2k_{\text{off}}c_{\mathrm{ava}_{\text{ret}}} - k_{\text{on}}c_{\mathrm{a}_{\text{ret}}}c_{\mathrm{va}_{\text{ret}}}) \qquad \text{in } \Omega_{\text{ret}}, t \in I \\
\frac{\mathrm{d}c_{\mathrm{ava}_{\text{ret}}}}{\mathrm{d}t} - D_{\mathrm{ava}_{\text{ret}}}\Delta c_{\mathrm{ava}_{\text{ret}}} &= -(2k_{\text{off}}c_{\mathrm{ava}_{\text{ret}}} - k_{\text{on}}c_{\mathrm{a}_{\text{ret}}}c_{\mathrm{va}_{\text{ret}}}) \qquad \text{in } \Omega_{\text{ret}}, t \in I.
\end{aligned}
$$

- Interface condition of the type:

$$
\begin{aligned}
-D\partial_{n_{\text{vit}}}c_{\mathrm{j}_{\text{vit}}} &= p_{\text{ILM}}(c_{\mathrm{j}_{\text{vit}}} - c_{\mathrm{j}_{\text{ret}}}) \text{ on } \Gamma_{\text{I}} \\
D\partial_{n_{\text{ret}}}c_{\mathrm{j}_{\text{ret}}} &= D\partial_{n_{\text{vit}}}c_{\mathrm{j}_{\text{vit}}} \qquad \text{on } \Gamma_{\text{I}}
\end{aligned}
$$

- Boundary: Neumann condition

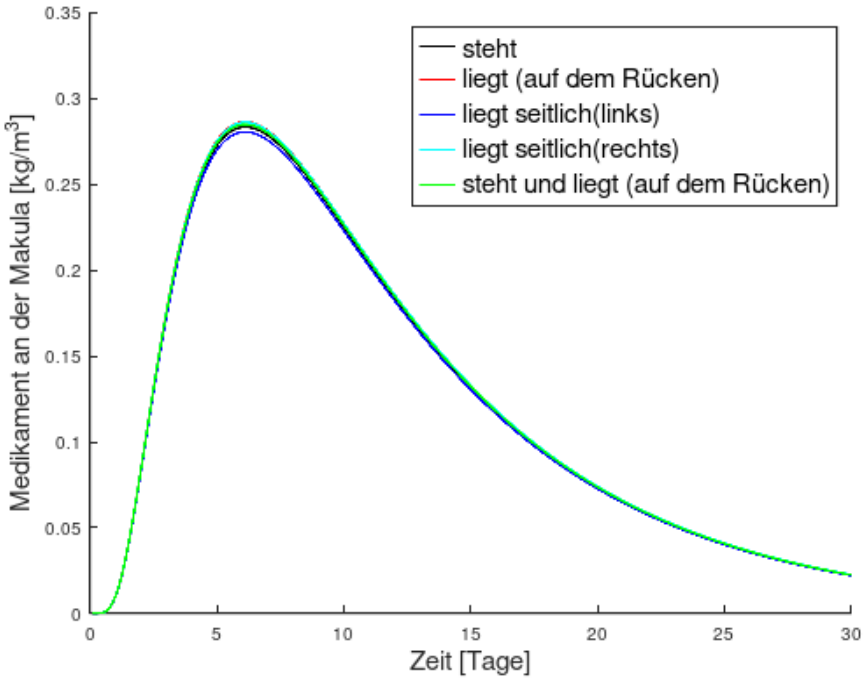
Concentrations after 0.5, 1 and 4.5 days



- The drug (anti-VEGF) distributes over time in the vitreous and slowly travels to the retina
- The VEGF concentration is higher in the retina than in the vitreous. Over time the VEGF in the retina decreases due to an increase of drug

Results

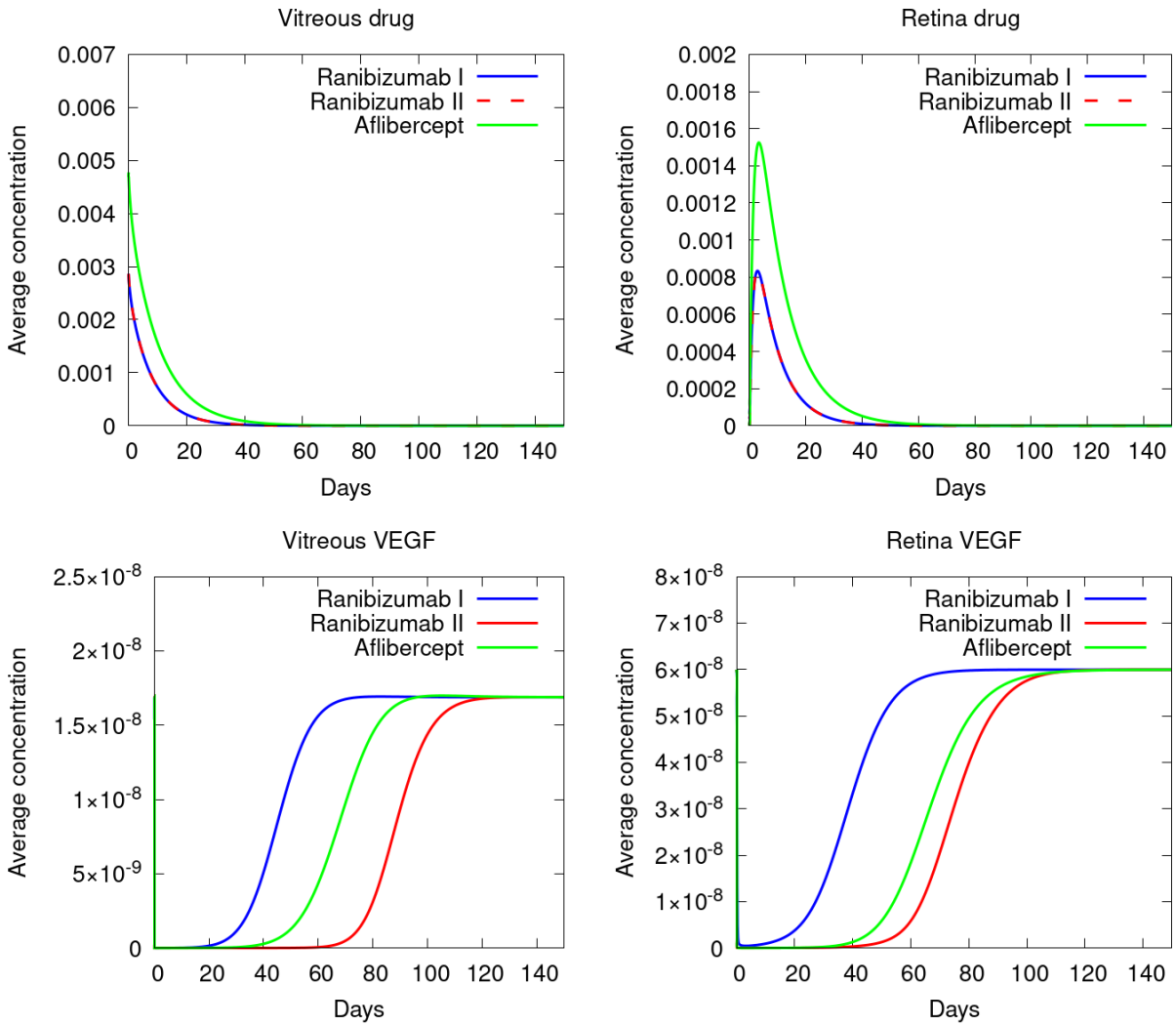
- the gravitation is neglectable



- The amount of drug reaching the macula depends on the injection position and time
- best pair of injection angles: $\psi_{xy} = 50°$, $\psi_z = 50°$

Results

- drug comparison: Lucentis (ranibizumab I, II) by Novartis vs Eylea (aflibercept) by Bayer



Conclusion

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Conclusion:

- Our presented models describe the geometry & physiology of the human eye
- Personalized models for the geometry of the eye & vitreous (pathological & healthy)
- We can test products from industry (pIOL)
- Drug therapy: pharmacological models & FE simulation
- Comparison of different drugs, their efficacy and different injection positions

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Thank you for your attention!