A Model of the Blood Flow in the Retina of the Eye

Edmond Rusjan
with
Andrea Dziubek, Giovanna Guidoboni, Alon Harris, Anil Hirani,
William Thistleton

SUNY Poly, IUPUI, University of Illinois at Urbana-Champaign

Vanderbilt, April 14, 2017

Abstract:

Understanding the blood flow in the retina of the eye may provide insights into several eye pathologies and ultimately lead to better treatments. We model the flow as a hierarchical Darcy flow on a curved surface and solve the model numerically using discrete exterior calculus and finite element exterior calculus. Results support the hypothesis that changes in the shape of the retina cause significant changes in the ocular blood flow, which may play a role in the dynamics of open angle glaucoma.

Outline

Modeling the Eye: Goals and Motivation

A Multiscale Model of Blood Flow in the Retina
- Hierarchical Darcy Flow
- Vascular Tree Architecture

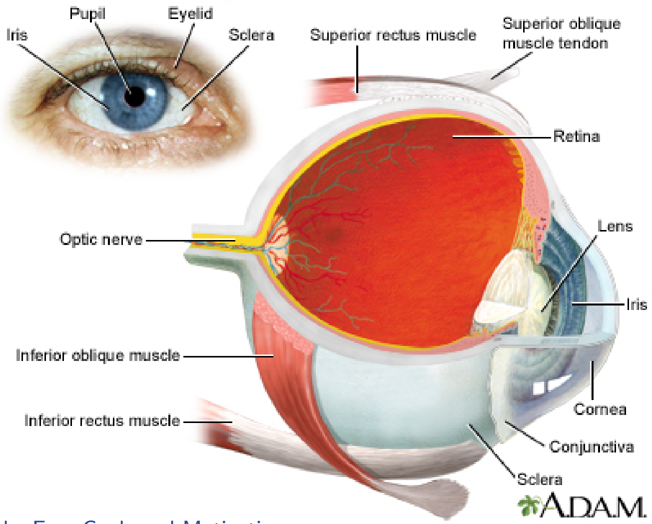
Computational Method
- Hierarchical Discretization
- Spatial Discretization
- Curved Surfaces
- Discrete Exterior Calculus (DEC) and Finite Element Exterior Calculus (FEEC)

Results
- Ocular Curvature May Play a Role in Glaucoma

Summary and Future Plans

The Eye

- The eye is the organ of sight: the sensory part is the retina.



Goals

- Advance the theory: most accurate models become theory
- Help reason: simplified models help us think more clearly
- Simulate experiments: experiments may be hard, or even impossible
- Competing goals: tension between simplicity and accuracy
- Solution: a collection of models at various levels of refinement

Motivation

- Preserve the vision
- Window into the body
- Part of the brain
- Opportunity to study flow on curved surfaces

Outline

Modeling the Eye: Goals and Motivation

A Multiscale Model of Blood Flow in the Retina
- Hierarchical Darcy Flow
- Vascular Tree Architecture

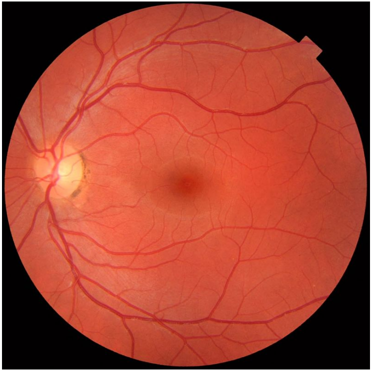
Computational Method
- Hierarchical Discretization
- Spatial Discretization
- Curved Surfaces
- Discrete Exterior Calculus (DEC) and Finite Element Exterior Calculus (FEEC)

Results
- Ocular Curvature May Play a Role in Glaucoma

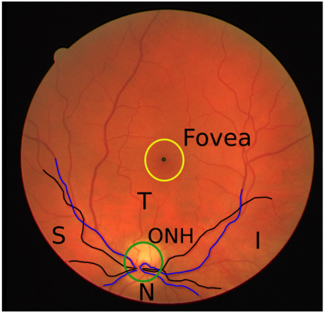
Summary and Future Plans

Fundus Images

- A healthy right eye (left) and a healthy left eye (right)



Regions of Particular Clinical Interest in the Retina



- optic nerve head (ONH)
- inferior quadrant (I)
- superior quadrant (S)
- nasal quadrant (N)
- temporal quadrant (T)
- fovea

i

- At the level of capillaries and small arterioles and venules, we don't see the details of the vascular tree architecture
- The tissue appears to be a porous medium
- Think of the vascular tree as a hierarchical structure
- Parameterize these hierarchical levels by a continuous parameter ϑ

Hierarchical Darcy Flow

- Consider averaged (smeared) quantities at position $\mathbf{x}$ in some spatial domain Ω for each hierarchy level ϑ
  - Velocity $\mathbf{v}(\mathbf{x},\vartheta)$
  - Hierarchical velocity $\omega(\mathbf{x},\vartheta)$
  - Pressure $p(\mathbf{x},\vartheta)$
- Model each ϑ level by Darcy flow equations and couple "vertically" with hierarchical flow

$$\begin{aligned}
\nabla\cdot(n_b\mathbf{v}) + \frac{\partial}{\partial\vartheta}(n_b\omega) &= 0 && \mathbf{x}\in\Omega, \vartheta\in(0,1)\\
n_b\mathbf{v} &= -\mathbf{K}\nabla p && \mathbf{x}\in\Omega, \vartheta\in(0,1)\\
n_b\omega &= -\alpha\frac{\partial p}{\partial\vartheta} && \mathbf{x}\in\Omega, \vartheta\in(0,1)
\end{aligned}$$

Parameters and Boundary Conditions

- Parameters
  - Tissue porosity $n_b(\mathbf{x}, \vartheta)$
  - Tissue perfusion $n_b\omega$
  - Tissue permeability tensor $\mathbf{K}(\mathbf{x}, \vartheta)$
  - Hierarchical permeability $\alpha(\mathbf{x}, \vartheta)$
  - Hydraulic conductivities G_v, G_a
  - Venous and arterial pressures $p_v(\mathbf{x})$ and $p_a(\mathbf{x})$
- Boundary conditions

$$\begin{aligned} n_b\omega(\mathbf{x}, 0) &= -G_v\left(p(\mathbf{x}, 0) - p_v(\mathbf{x})\right) && \mathbf{x} \in \Omega \\ n_b\omega(\mathbf{x}, 1) &= -G_a\left(p_a(\mathbf{x}) - p(\mathbf{x}, 1)\right) && \mathbf{x} \in \Omega \\ n_b\mathbf{v}(\mathbf{x}, \vartheta) \cdot \mathbf{n} &= 0 && \mathbf{x} \in \partial\Omega, \vartheta \in [0,1] \end{aligned}$$

- Couple to feeding arteries and draining veins

$$G_v = \alpha_v \delta_v(\mathbf{x}) \quad \text{and} \quad G_a = \alpha_a \delta_a(\mathbf{x})$$

- α_v and α_a are venous and arterial conductances

Vascular Tree Architecture

- $\delta_v(\mathbf{x})$ and $\delta_a(\mathbf{x})$ are delta functions which differ from zero only where the feeding arteries and draining veins are located, respectively
- Need to extract feeding arteries and draining veins from fundus images
- Alternatively, model the vascular tree
- Young (1808): Compare parent and daughters vessels
  - Assume two identical daughters
  - Radius ratio: $\frac{r_p}{r_d} = 2^{\frac{1}{3}} = 1.26$
  - Area ratio: $\frac{A_p}{A_d} = 2^{-\frac{1}{3}}$
- Murray (1926): Generalize to asymmetric trees
  - Similar to Pythagora, except cubes: $r_p^3 = \sum r_d^3$
  - Derives from optimality (variational principle)
- Forgotten for many years, then "rediscovered"

Optimal Transport $\implies$ Murray's Law

- P_f power needed to maintain the blood flow (viscous losses)
- P_m power needed to metabolically maintain the blood and the vessel
- $P_t = P_f + P_m$ total power
- Minimize P_t!
- Assume cylindrical vessels: $f = cp$
  - f is volumetric flow rate
  - p is pressure difference
  - c is conductance coefficient
- Assume Poiseuille flow: $c = \frac{\pi r^4}{8\mu l}$
  - μ is blood viscosity
  - l is vessel length
- Min $P_f = pf = af^2 r^{-4} \implies r \to \infty$?
  - $a = \frac{8\mu l}{\pi}$
- Min $P_m = mV = m\pi r^2 l = br^2 \implies r \to 0$?
  - m is a metabolic coefficient
  - $b = m\pi l$
- Min $P_t \implies \frac{dP_t}{dr} = 0 \implies -4af^2 r^{-5} + 2br = 0 \implies f = kr^3$!
  - $k = (\frac{b}{2a})^{1/2}$

Recent Experimental Data and Models

- Takahashi (2009, 2013): $f = kr^m$
  - Theory (Murray): $m = 3$
  - Data (Takahashi 2009): $m \approx 2.85$
  - Data (Takahashi 2013): significant deviations in m between various organs
- In addition to radius, interested in length and angle
  - Theory: open problem!
  - Data: rather scarce - open problem!
  - Model (Takahashi 2009): $L = 7.4r^{1.15}$
- Open question: what optimality?

Outline

Modeling the Eye: Goals and Motivation

A Multiscale Model of Blood Flow in the Retina
- Hierarchical Darcy Flow
- Vascular Tree Architecture

Computational Method
- Hierarchical Discretization
- Spatial Discretization
- Curved Surfaces
- Discrete Exterior Calculus (DEC) and Finite Element Exterior Calculus (FEEC)

Results
- Ocular Curvature May Play a Role in Glaucoma

Summary and Future Plans

Hierarchical Discretization

- Standard FE procedure
- Rewrite in weak form
- Introduce piecewise linear basis functions $\{\varphi_i\}$ with $i = 0, .., n$ on $[0, 1]$ corresponding to nodes $\{\theta_i\}$ and we let $\varphi = \varphi_i$.
- We assume permeabilities and pressure are piecewise linear interpolations of the hierarchical variable

$$\mathbf{K}(\mathbf{x}, \theta) = \sum_{k=0}^{n} \mathbf{K}(\mathbf{x}, \theta_k)\varphi_k(\theta), \quad \alpha(\mathbf{x}, \theta) = \sum_{k=0}^{n} \alpha(\mathbf{x}, \theta_k)\varphi_k(\theta),$$

$$p(\mathbf{x}, \theta) = \sum_{k=0}^{n} p(\mathbf{x}, \theta_k)\varphi_k(\theta)$$

-

$$-\sum_{j=0}^{n} \int_\Omega \Big(\mathbf{K}_{ij}(\mathbf{x})\nabla p_j(\mathbf{x}), \nabla q(\mathbf{x})\Big)\, \mathrm{d}\mathbf{x} - \sum_{j=0}^{n} \int_\Omega \alpha_{ij}(\mathbf{x})\, p_j(\mathbf{x})\, q(\mathbf{x})\, \mathrm{d}\mathbf{x}$$

$$= \int_\Omega f_i(\mathbf{x})\, q(\mathbf{x})\, \mathrm{d}\mathbf{x}$$

Hierarchical Discretization Cont.

- where

$$\begin{aligned}
\mathbf{K}_{ij}(\mathbf{x}) &= \sum_{k=0}^{n} \mathbf{K}(\mathbf{x}, \theta_k) \int_{[0,1]} \varphi_k(\theta)\, \varphi_i(\theta)\, \varphi_j(\theta)\, \mathsf{d}\theta \\
\alpha_{ij}(\mathbf{x}) &= \sum_{k=0}^{n} \alpha(\mathbf{x}, \theta_k) \int_{[0,1]} \varphi_k(\theta)\, \frac{\partial \varphi_i(\theta)}{\partial \theta}\, \frac{\partial \varphi_j(\theta)}{\partial \theta}\, \mathsf{d}\theta \\
f_i(\mathbf{x}) &= \alpha_v p_v \delta_{i0} + \alpha_a p_a \delta_{in}
\end{aligned} \tag{1}$$

- The **hierarchical discretization** leads to a tridiagonal system for the pressures $p_i(\mathbf{x}, \theta_i)$.

Example: 3 layer model

- For three levels $i = 0, 1, 2$ and with isotropic and space independent permeability $\mathbf{K}_{ij} = K_{ij}\mathbf{I}$ per level we have $\nabla \cdot \mathbf{K}_{ij} \nabla = K_{ij} \Delta$
- This yields

$$
-\begin{bmatrix} K_{00}\Delta + \alpha_{00} & K_{01}\Delta + \alpha_{01} & \\ K_{10}\Delta + \alpha_{10} & K_{11}\Delta + \alpha_{11} & K_{12}\Delta + \alpha_{12} \\ & K_{21}\Delta + \alpha_{21} & K_{22}\Delta + \alpha_{22} \end{bmatrix} \begin{bmatrix} p_0 \\ p_1 \\ p_2 \end{bmatrix} = \begin{bmatrix} f_0 \\ f_1 \\ f_2 \end{bmatrix}. \tag{2}
$$

- Permeability matrix K_{ij}, conductivity matrix α_{ij}, and right hand side vector f_i as given in equation (1).

The K and α matrices in the 3 layer model

- The scalar K_{ij} is the ij entry of the matrix

$$\frac{1}{24}\begin{bmatrix} 3K_0+K_1 & K_0+K_1 & 0 \\ K_0+K_1 & K_0+6K_1+K_2 & K_1+K_2 \\ 0 & K_1+K_2 & K_1+3K_2 \end{bmatrix},$$

- The scalar α_{ij} is the ij entry of the matrix

$$\begin{bmatrix} \alpha_0+\alpha_1+G_v & -(\alpha_0+\alpha_1) & 0 \\ -(\alpha_0+\alpha_1) & \alpha_0+2\alpha_1+\alpha_2 & -(\alpha_1+\alpha_2) \\ 0 & -(\alpha_1+\alpha_2) & \alpha_1+\alpha_2+G_a \end{bmatrix},$$

- The scalar f_i is the i component of the vector

$$\left[G_v p_v, 0, G_a p_a\right]^T.$$

  Here $\alpha_0, \alpha_1, \alpha_2$ and K_0, K_1, K_2 are the conductivities and permeabilities at the three hierarchical levels and are given in equation (1).

Exterior Algebra

- Motivation: generalize the cross product $\times$ from $\mathbb{R}^3$ to $\mathbb{R}^n$
- V an n dimensional real vector space with elements u, v, ...
- $u \wedge v$ exterior (wedge) product of u and v
  - anti-symmetric: $u \wedge v = -v \wedge u$
  - linear in each factor: $(au + bv) \wedge w = au \wedge w + bv \wedge w$
- $\bigwedge^0 V = \mathbb{R}$
- $\bigwedge^1 V = V$
- $\bigwedge^2 V = V \bigwedge V$, 2-vectors
- continue recursively, demanding associativity
- $\bigwedge^p V$ p-vectors, $dim(\bigwedge^p V) = \binom{n}{p}$
- $dim(\bigwedge^n V) = 1$
- V inner product space:
  - natural isomorphism between V and its dual V^*
  - flat: $\flat : V \to V^*$, $u^\flat(v) = (u, v)$
  - sharp: $\sharp : V^* \to V$, $\sharp = \flat^{-1}$
  - inner product on V induces inner product on $\bigwedge^p V$ (the notion of length induces notions of area, volume, p-volume)

Hodge $*$

- Motivation: $u \wedge v$ is a 2-vector, so not quite $u \times v$ yet
- Solution: so map $u \wedge v$ to $u \times v$ - call this map Hodge $*$
- Then: $u \times v = *(u \wedge v)$
- V oriented inner product space: $* : \bigwedge^p V \to \bigwedge^{(n-p)} V$
- natural isomorphism
- Let $\{e_1, e_2, \ldots, e_n\}$ be a basis for V
- Let $\sigma = e_1 \wedge e_2 \wedge \cdots \wedge e_n$ be a chosen orientation
- Hodge $*$: $u \wedge v = (*u, v)\sigma, \quad \forall v \in \bigwedge^{(n-p)} V$
- Intuition: complementary $n - p$ vector to the given p vector
  - orthogonal
  - consistent with the orientation
- Side result: $u \cdot v = (u, v) = *(u \wedge *v) = *(v \wedge *u)$

Hodge $*$ Example

- $V = \mathbb{R}^2$:

$$\begin{array}{ccc} *1 & = & e_1 \wedge e_2 \\ *e_1 & = & e_2 \\ *e_2 & = & -e_1 \\ *(e_1 \wedge e_2) & = & 1 \end{array}$$

- $V = \mathbb{R}^3$:

$$\begin{array}{ccc} *1 & = & e_1 \wedge e_2 \wedge e_3 \\ *e_1 & = & e_2 \wedge e_3 \\ \dots & = & \dots \\ *(e_1 \wedge e_2) & = & e_3 \\ \dots & = & \dots \\ *(e_1 \wedge e_2 \wedge e_3) & = & 1 \end{array}$$

Exterior Calculus

- Differential forms - generalizations of differentials
  - Let M be a manifold
  - 0-forms are functions
  - 1-forms are differentials
  - k-forms at a point P are k vectors (elements in $\bigwedge^k T_P^* M$)
- Exterior Derivative d
  - $df = \frac{\partial f}{\partial x^i} dx^i$
  - $d(f dx^1 \wedge \cdots \wedge dx^k) = df \wedge dx^1 \wedge \cdots \wedge dx^k$
- Adjoint derivative: $\delta = *d*$, with $(\delta\alpha, \beta) = (\alpha, d\beta)$
- Laplacian: $\Delta = (d + \delta)^2$
- Interior Product: $(i_X \alpha)(v_2, \ldots, v_k) = \alpha(X, v_2, \ldots, v_k)$
- Lie Derivative (using Cartan's Magic Formula):
  $L_X \alpha = d i_X \alpha + i_X d\alpha$

Curved Surfaces

- Numerically, a major issue is: retina is a curved surface
- Flat: $(\frac{\partial}{\partial x^i})^\flat = g_{ij}dx^j$, $(v^\flat)_i = g_{ij}v^j$
- Sharp: $(dx^i)^\sharp = g^{ij}\frac{\partial}{\partial x^j}$
- Hodge $*$: $(*\alpha)_{i_1,i_2,\ldots,i_{n-k}} = \frac{1}{k!}\alpha^{j_1,\ldots,j_k}\sqrt{\det g}\,\epsilon_{j_1,\ldots,j_k,i_1,\ldots,i_{n-k}}$

Algebraic Topology Approach to Space Discretization

- Simplices
- Simplicial Complexes
- Chains
- Cochains
- Boundary operator ∂
- Discrete exterior derivative $D = \partial^T$
- Discrete version of Stokes theorem

M^{DEC}: DEC Hodge *

- Marsden, Hirani, Desbrun, et al.: $\frac{1}{|*\sigma|}\int_{*\sigma} *\alpha = \frac{1}{|\sigma|}\int_{\sigma}\alpha$
- $[M^{DEC}]_{ij} = \frac{|*\sigma_i^k|}{|\sigma_i^k|}\delta_{ij}$
- Advantage: M^{DEC} diagonal
- Disadvantage: M^{DEC} not positive definite, because circumcenter may be outside the simplex
- Example: standard 2-simplex; vertices: $(0,0)$, $(1,0)$, $(0,1)$

$$M_1^{DEC} = \begin{bmatrix} \frac{1}{2} & 0 & 0 \\ 0 & \frac{1}{2} & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

M^{Whit}: FEEC Hodge *

- Arnold, Falk, Winther.
- Whitney 0-forms are barycentric coordinates:
- Whitney 1-forms: $\eta_k = \lambda_i d\lambda_j - \lambda_j d\lambda_i$
- $[M^{Whit}]_{ij} = \int \eta_i \eta_j dA$
- Advantage: M^{Whit} is positive definite, because barycenter is always inside the simplex
- Disadvantage: M^{Whit} not diagonal, $(M^{Whit})^{-1}$ not sparse
- Example: standard 2-simplex; vertices: $(0,0)$, $(1,0)$, $(0,1)$

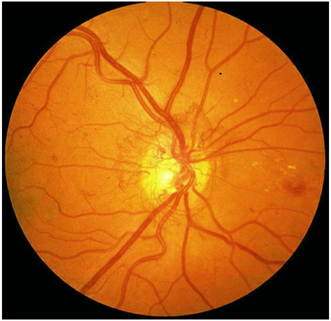
$$M_1^{Whit} = \begin{bmatrix} \frac{1}{3} & \frac{1}{6} & 0 \\ \frac{1}{6} & \frac{1}{3} & 0 \\ 0 & 0 & \frac{1}{6} \end{bmatrix}$$

PyDEC - A Python Implementation of DEC

- Authors: Hirani and Bell
- Efficient operator implementation in terms of sparse matrices
- Data structures
  - Simplicial Complex
  - Regular Cube Complex
- Operators
  - Discrete Exterior Derivative
  - Diagonal Sparse Matrix Discrete Hodge $*$
  - First Order Whitney Hodge $*$
- Provides a nice playground for numerical experiments

Data

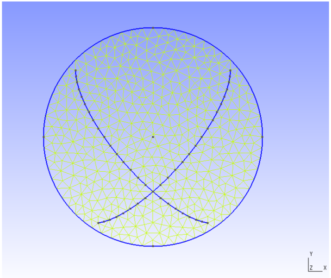
Figure: Retina Fundus Image



webvision.med.utah.edu/book/part-i-foundations/simple-anatomy-of-the-retina/

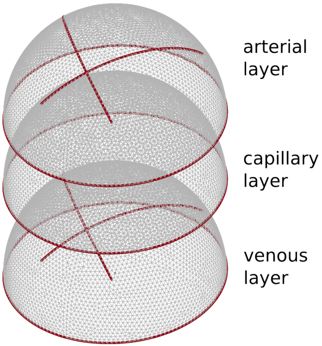
Spatial Discretization

Figure: Triangularization by gmsh.



Example: 3 layer model geometry

Figure: Three layer discretization



The $\theta = 1$ layer represents arterioles, the $\theta = \frac{1}{2}$ layer represents capillaries and $\theta = 0$ represents venules.

Outline

Modeling the Eye: Goals and Motivation

A Multiscale Model of Blood Flow in the Retina
- Hierarchical Darcy Flow
- Vascular Tree Architecture

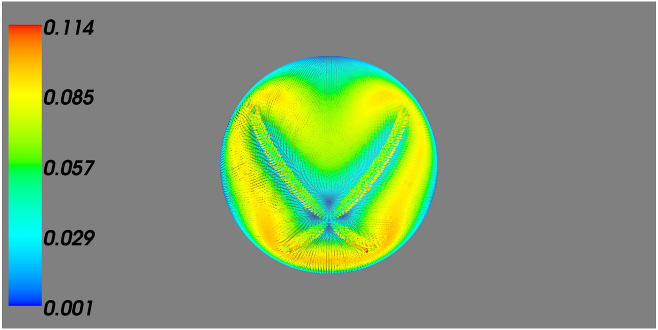
Computational Method
- Hierarchical Discretization
- Spatial Discretization
- Curved Surfaces
- Discrete Exterior Calculus (DEC) and Finite Element Exterior Calculus (FEEC)

Results
- Ocular Curvature May Play a Role in Glaucoma

Summary and Future Plans

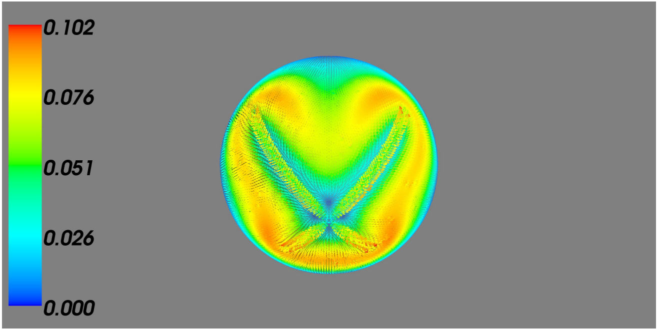
Capillary Velocity Field

Figure: Capillary Blood Velocity



Application: Myopia

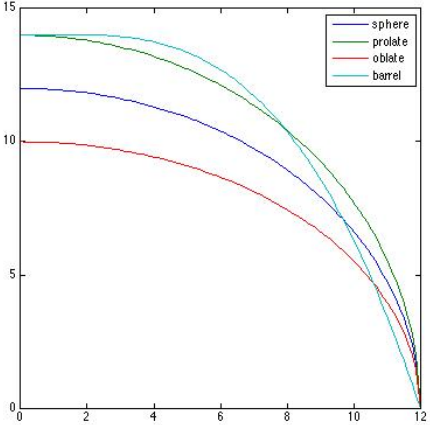
Figure: Capillary Blood Velocity in Myopia



The myopic eye is extended along the optical axis.

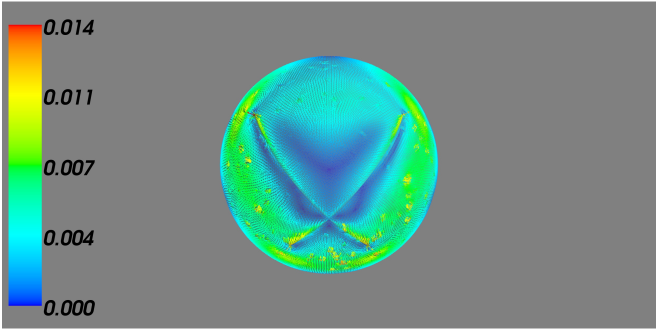
Eye Deformations

Figure: Eye Shapes



Velocity Field Deformations

Figure: Velocity Difference



Caution: to compare the velocity field difference in a meaningful way, all velocity fields are first pulled back to the sphere.

Outline

Modeling the Eye: Goals and Motivation

A Multiscale Model of Blood Flow in the Retina
- Hierarchical Darcy Flow
- Vascular Tree Architecture

Computational Method
- Hierarchical Discretization
- Spatial Discretization
- Curved Surfaces
- Discrete Exterior Calculus (DEC) and Finite Element Exterior Calculus (FEEC)

Results
- Ocular Curvature May Play a Role in Glaucoma

Summary and Future Plans

Summary

- The hierarchical Darcy equation models blood flow in the retina as a hierarchical porous medium.
- Exterior Calculus generalizes vector calculus to manifold and is convenient for formulating and solving models on surfaces.
- The discrete exterior derivative d is unique and determined by the discrete Stokes theorem.
- The discrete Hodge * operator is an open question and a topic of current research.
- DEC and FEEC are related; they differ in the Hodge * discretization.
- DEC and FEEC can be mixed with traditional FEs.
- Curvature may play an important role in the development of glaucoma.

Future Plans

- Generalize the model to space dependent parameters.
- Couple the model with elasticity.
- Use the model to make predictions for other eye pathologies.
- The eye is the window into the body. What can we learn about conditions in the rest of the body?
- Personalized medicine: couple the model with image analysis front end.

Acknowledgments

- NSF DMS-1224195 and NSF CCF-1064429
- NIH 1R21EY022101-01A1
- Slocum Dickson Foundation
- Research to Prevent Blindness (RPB, NY, USA)
- Indiana University Collaborative Research Grant of the Office of the Vice President for Research
- Chair Gutenberg funds
- SUNY STEM Summer Research
- SUNY Poly School of Arts and Sciences

References

- Abraham, Marsden, Ratiu, Manifolds, Tensor Analysis and Applications.
- Flanders, Differential Forms with Applications to the Physical Sciences.
- Frankel, The Geometry of Physics.
- T. Sherman, On Connecting Large Vessels to Small, The Meaning of Murray's Law, J. Gen. Phisiol, 78, 431-453, (1981).
- T. Takahashi et. al., A mathematical model for the distribution of hemodynamic parameters in the human retinal microvascular network, J. Biorrheol, 23, 77-86, (2009).
- Desbrun, A. N. Hirani, J. E. Marsden: *Discrete Exterior Calculus for Variational Problems in Computer Graphics and Vision*, Proceedings of the 42nd IEEE Conference on Decision and Control, Honolulu 5 (2003), 9–12.
- Arnold D., Falk R., Winther R. : *Finite Element Exterior Calculus: from Hodge Theory to Numerical Stability*, Bull. Amer. Math. Soc. 47,2 (2010), 281–354.

References Cont.

- Anil N. Hirani and Kaushik Kalyanaraman: *Numerical Experiments for Darcy Flow on a Surface Using Mixed Exterior Calculus Methods*, E-print arXiv:1103.4865v1 [cs.NA] on arxiv.org (2011).
- A. N. Hirani, K. B. Nakshatrala, J. H. Chaudhry: *Numerical method for Darcy flow derived using Discrete Exterior Calculus*, E-print arXiv:0810.3434 [math.NA] on arxiv.org (2008)
- Nathan Bell and Anil N. Hirani: *PyDEC: Software and Algorithms for Discretization of Exterior Calculus*, ACM Transactions on Mathematical Software, Vol 39 1 (2012), 1–289.
- A. Dziubek, E. Rusjan, W. Thistleton: *Challenges in Blood Flow Simulation: Numerical Methods and Image Processing Tools*, Proceedings of the ASME/FDA, 1st Annual Frontiers in Medical Devices, Washington DC (2013).
- A. Dziubek, G. Guidoboni, A. Harris, A.H. Hirani, E. Rusjan, W. Thistleton, *Effect of ocular shape and vascular geometry on retinal hemodynamics: a computational model*, Biomechanics and Modeling in Mechanobiology (2015), 1-15.

Thank You!