1B P8: Bioengineering

Ocular Biomechanics and Biomaterials

Lecturer: Prof Yan Yan Shery Huang (yysh2)

Biomechanics course outlines

1. Tissues in the Eye
   - Normal eye anatomy
   - Composition and structure of tissues
   - Biomaterial mechanical properties

2. Structural and Fluid Mechanics
   - The eye as a shell
   - Flow of blood and aqueous humour
   - IOP; Modelling glaucoma

3. Disorder, Disease and Repair
   - Disorder in focal function
   - Contact and intraocular lenses
   - Cataracts, corneal opacity
   - Tissue engineering for eye repair

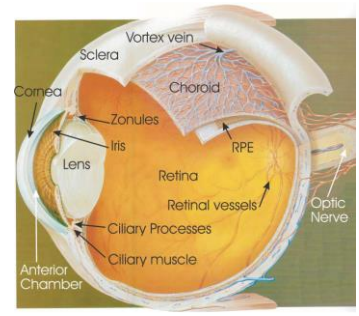
Define the problem

↓

When to apply Engineering & **How** to solve

↓

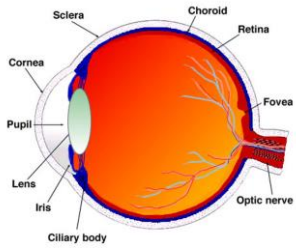
What is the broader impact

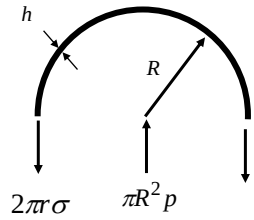


The eye as a pressurised shell

[Model simplifications; assumptions]

- Need to maintain shape to preserve optical properties.
- Shape maintained by internal pressurisation - intraocular pressure (IOP).
- Overall structure can be represented as a thin-walled spherical shell.
- Wall properties given by sclera and cornea.
- Structural features at cornea and at optic nerve omitted
- Tissue property is linear elastic and time-independent
- Model as a sphere with no bending stresses to give biaxial stresses:



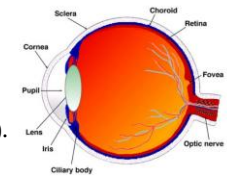


$$\frac{\sigma}{p} = \frac{R}{2h}$$

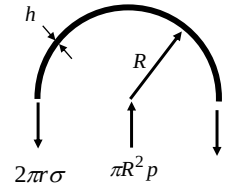
3

The eye as a pressurised shell

[Model simplifications; assumptions]



- Need to maintain shape to preserve optical properties.
- Shape maintained by internal pressurisation - intraocular pressure (IOP).
- Values of IOP (NB 1 mmHg = 133 Pa)
  - Normal = 15.5 mmHg
  - Changes with arterial pulse
  - Extreme = 50 mmHg
  - Loads due to accommodation (changing lens shape), blinking
  - Rubbing eyes, IOP ~80 mmHg.
- Overall structure can be represented as a thin-walled spherical shell.
- Wall properties given by sclera and cornea.
- Structural features at cornea and at optic nerve.
- Model as a sphere with no bending stresses to give biaxial stresses:
- e.g. p =15.5 mmHg, h = 0.78 mm, R = 12 mm, E = 3 MPa



$$\frac{\sigma}{p} = \frac{R}{2h}$$

Analyse the equation

$\sigma = 16\,\text{kPa}$ $\quad \varepsilon = \frac{\sigma}{E}(1-\nu) \approx \frac{\sigma}{2E} = 0.26\%$

Implications: change in eye size during different loads, failure?

4

Structure: Ocular rigidity

- Rigidity important in understanding of measurement of IOP (tonometry), resistance to aqueous humour outflow, development of myopia (near sightedness), ocular pulse.
- Assume linear relationship between biaxial wall stress σ and strain ε: $\varepsilon = \frac{\sigma(1-\upsilon)}{E}$
- Change in volume V related to change in radius and strain: $V = \frac{4\pi R^3}{3} \Rightarrow \frac{\mathrm{d}V}{V} = \frac{3\mathrm{d}R}{R} = 3\mathrm{d}\varepsilon$
- Wall stresses proportional to IOP as per shell calculation — for small ε

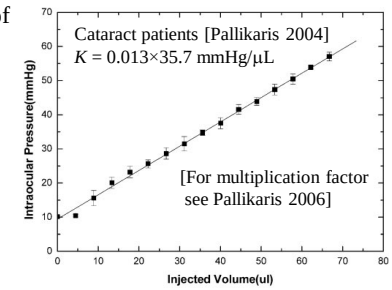
$$\frac{\sigma}{IOP} = \frac{R}{2h} \Rightarrow \frac{\mathrm{d}\sigma}{\mathrm{d}(IOP)} = \frac{R}{2h}$$

neglecting second order change of R

- The coefficient of rigidity K characterises the effect of IOP on change in volume. It is a structural property, depending on geometry and material properties.

$$\frac{\mathrm{d}(IOP)}{\mathrm{d}V} \equiv K = \frac{\mathrm{d}(IOP)}{\mathrm{d}\sigma}\frac{\mathrm{d}\sigma}{\mathrm{d}\varepsilon}\frac{\mathrm{d}\varepsilon}{\mathrm{d}V} = \frac{2h}{R}\frac{E}{(1-\upsilon)}\frac{1}{3V}$$

- Typical values of h = 0.78mm, R = 12 mm, E = 3 MPa, ν = 0.5, give K = 0.27 mmHg/μL, in good agreement with the measured value of 0.46 mmHg/μL.



5

Tonometry [Biomechanics as a diagnostic tool]

[Ethier and Simmons]

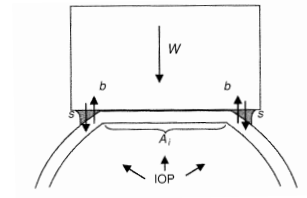
- Changes in IOP are implicated in disease, e.g. glaucoma.
- Tonometry measures IOP indirectly by deformation of the cornea.
- Direct measurement of pressure by e.g. pressure tapping not normally appropriate.

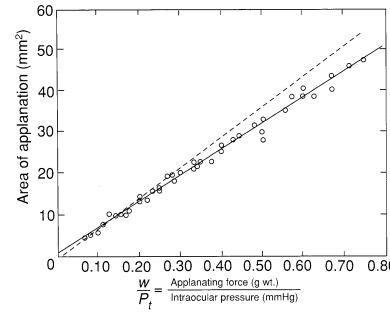
https://vimeo.com/75806361

6

Tonometry [Biomechanics as a diagnostic tool]

- Goldmann tonometry:
  - anaesthetize cornea
  - place head on cornea with force *W*
  - flattened area *A*
  - IOP = *W*/*A*
  - correction needed for tear film and bending stresses
  - empirically noted that these cancel out when $A = 7.35\ mm^2$
  - further correction for abnormal corneal thickness.
- Changes in IOP associated with elastic deformation and outflow of aqueous humour





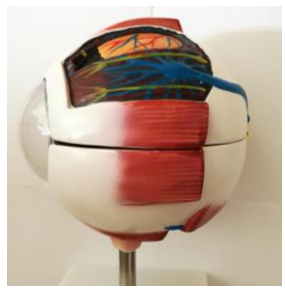
[Ethier and Simmons]

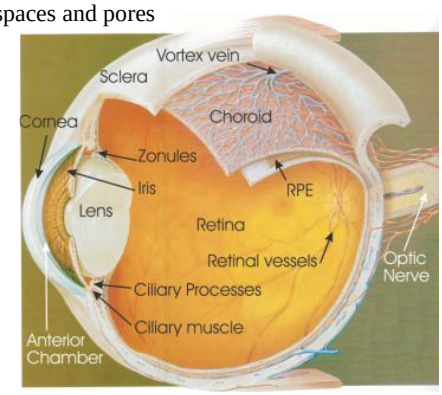
7

Fluid: Fluids in the eye

Fluid type: blood flow; aqueous humour; interstitial flow in ECM;

- No vasculature in the lens and cornea to ensure transparency – the aqueous humour nourishes these regions.
- Blood transports oxygen and nutrients, taking away waste products.
- Choroid has highest perfused volume of any tissue in body – high metabolism needed to detect photons.
- Interstitial fluids: fluids contained in all tissue spaces and pores



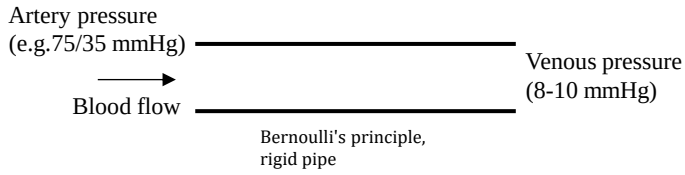


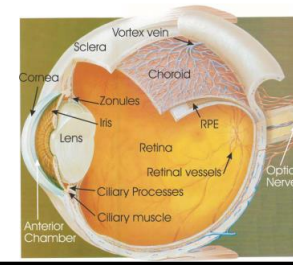
8

Blood flow in the eye

- Unique blood flow system in eye.
- Blood transports oxygen and nutrients, taking away waste products.
- Choroid has highest perfused volume of any tissue in body – high metabolism needed to detect photons.
- "Starling resistor":
  - Pressure falls along vessel due to pipe friction

[Model simplifications; assumptions]



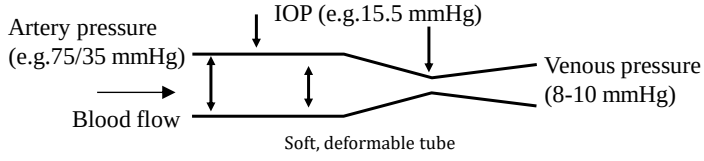


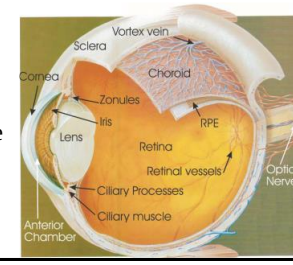
9

Blood flow in the eye

- Unique blood flow system in eye.
- Blood transports oxygen and nutrients, taking away waste products.
- Choroid has highest perfused volume of any tissue in body – high metabolism needed to detect photons.
- "Starling resistor":
  - Pressure falls along vessel due to pipe friction
  - Collapse of blood vessel under external pressure causes constriction
  - Constriction controls flow, with no effect of downstream pressure on flow
  - Compares with supersonic throat or waterfall – hence termed vascular waterfall
  - Net effect: flow controlled by IOP rather than venous pressure
  - Need to autoregulate flow to cope with differences in IOP.

[Model simplifications; assumptions]



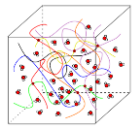


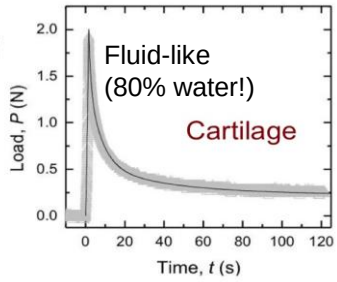
10

Fluid flow in tissue: A Poroelasticity Model

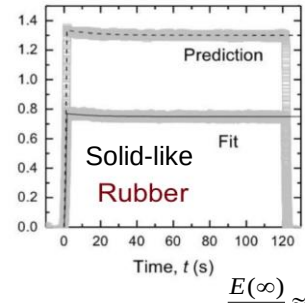
[Model simplifications; assumptions]

Step displacement input

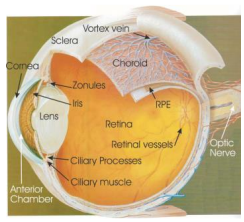




$$\frac{E(\infty)}{E(0)} << 1$$



$$\frac{E(\infty)}{E(0)} \approx 1$$



Time dependent material response

Simplest model of such behaviour: linear poroelastic theory

Solid phase is linearly elastic and isotropic

All time-dependence is due to flow of fluid through the porous matrix

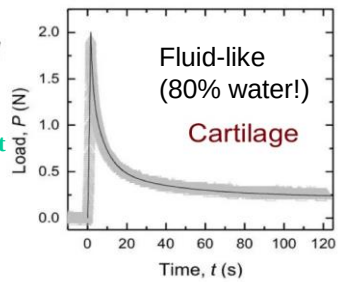
In the context of extracellular matrix (ECM) → *interstitial flow in ECM*

11

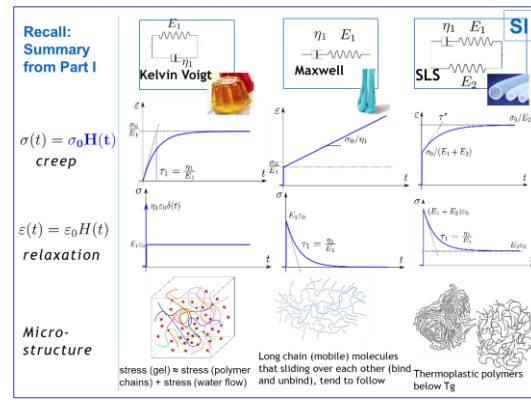
Fluid flow in tissue: A Poroelasticity Model

[Model simplifications; assumptions]

Step displacement input



$$\frac{E(\infty)}{E(0)} << 1$$



Time dependent material response

Simplest model of such behaviour: linear poroelastic theory

Solid phase is linearly elastic and isotropic

All time-dependence is due to flow of fluid through the porous matrix

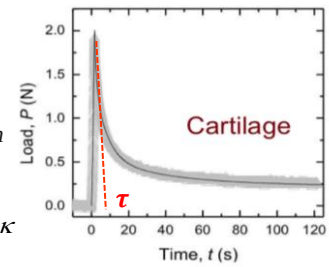
12

Characterising poroelastic flow

Step pressure input

Darcy's Law for fluid flow: $Q = \frac{\kappa A(\Delta p)}{h}$

Step displacement input



Q = rate of volume discharge across an area, A

Δp = pressure difference applied across specimen with thickness h

κ = hydraulic permeability [units m^4 $(Ns)^{-1}$]

Microstructural interpretation - Intrinsic permeability k: $k = \eta\kappa$

η = fluid viscosity, 1 mPa s for water, 0.75 mPas for aqueous humour (NB η not fluids symbol of μ to avoid confusion with friction).

k has units of m^2 and gives an estimate of internal surface areas covered by the pores → the intrinsic pore size

Pore sizes can be too small to see (nm) but can be measured mechanically $\tau = \frac{h^2}{E\kappa}$

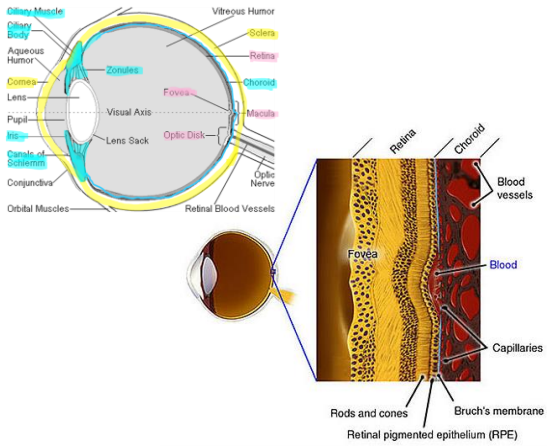
Time constant:

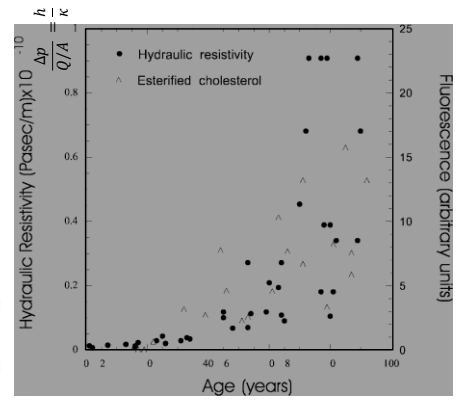
e.g. dimensional analysis

13

Applying Darcy's Law (to understand disease mechanism)

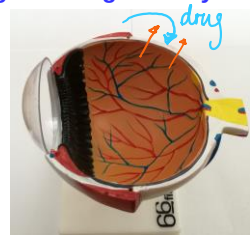
- **Bruch's membrane** is a five-layer barrier limiting transport between the choroid and the outer retina.
- Water moves under the action of hydrostatic and osmotic pressure gradients.
- Increase in hydraulic resistance with age a consequence of lipid accumulation, hypothesized to contribute to age-related macular degeneration by causing retinal detachment.

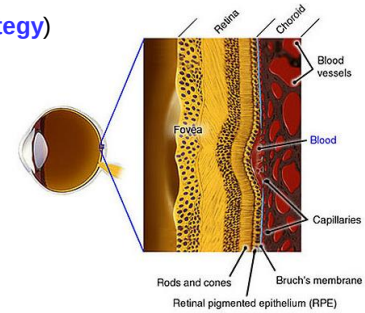




14

Applying Darcy's Law (to guide drug delivery strategy)





- Corneal drug delivery difficult.
- **Scleral drug delivery** to retina may be attractive; need to check on transport rates.
- Compare fluid transport in the opposite directions: due to convection flow (Darcy's law) vs. diffusional transport
- Dimensional analysis

$\kappa \Delta p$ (unit, m^2/ s), Darcy's law κ = hydraulic permeability [units m^4 $(Ns)^{-1}$]

D (unit, m^2/ s), diffusion coefficient

$\eta = 7.5\times10^{-4}$Pa.s, Δp=15 mmHg, intrinsic permeability $k = 2\times10^{-14}cm^2$
[NB easiest to convert to SI units first, and check dimensions]

→ $\kappa \Delta p \sim 5\times10^{-12}$ m^2/s

→ $D \sim 2\times10^{-10}$ m^2/s to ~ 4×10^{-13} m^2/s

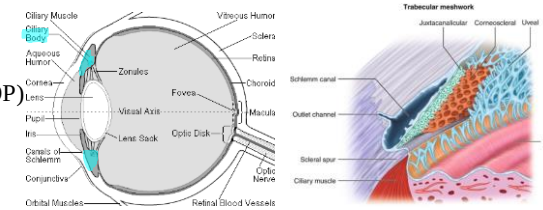
Solute	Mol. wt.	K(cm²/hr) at 37 C	Obstruction
$S^{35}CN^-$		(0·8–1·85) $\times 10^{-2}$	7
^{22}Na		(1·0–1·6) $\times 10^{-2}$	6
Pilocarpine	208	(2·8–4·4) $\times 10^{-3}$	7·5
Penicillin G	372	(1·8–2·0) $\times 10^{-3}$	12·5
Hydrocortisone (^3H)	460	(1·25–2·5) $\times 10^{-3}$	12
Inulin (^{14}C)	5000	(3·6–7·1) $\times 10^{-4}$	16
Hemoglobin	65 000	(4–17) $\times 10^{-5}$	40
RISA (^{125}I)	69 000	(2·2–5·4) $\times 10^{-5}$	80

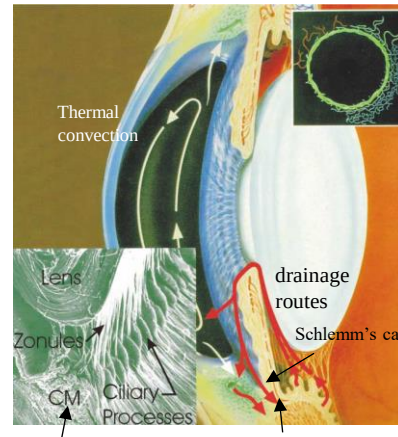
https://doi.org/10.1016/0014-4835(77)90136-1

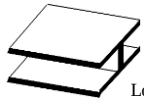
15

Aqueous humour flow regulation

- Provides pressurisation of eye (source of IOP)
- Nourishes cornea and lens
- Clears debris from eye (e.g. red cells from haemorrhage)
- Typical production rate of 2.4 µL/min – 1% of volume of anterior chamber per minute, peak in morning, minimum at night







Structure (anatomy)

Material (living, reactive)

Loading conditions

State of the material: functions, deformation, failure

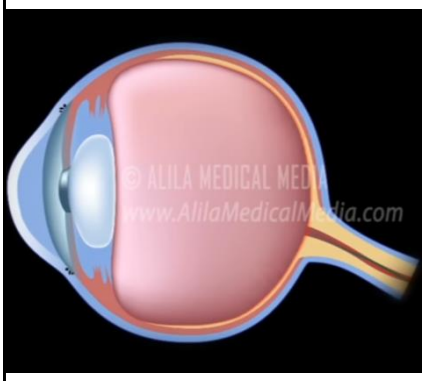
Concept: Mechanobiology

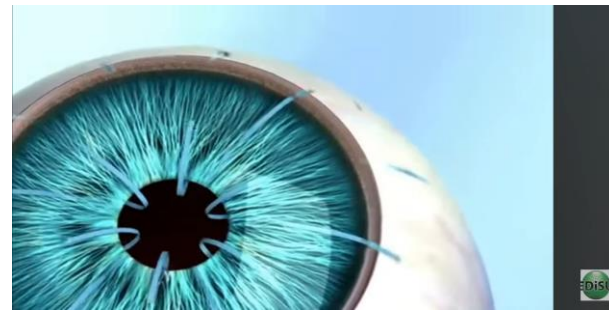
Source: https://link.springer.com/chapter/10.1007/978-981-15-5632-6_2

[Ethier et al]

16

Aqueous humour flow regulation





Source: https://www.youtube.com/watch?v=TgjdPgSxeYg;
https://www.centreforsight.com/treatments/glaucoma-treatments-migs/hydrus

17

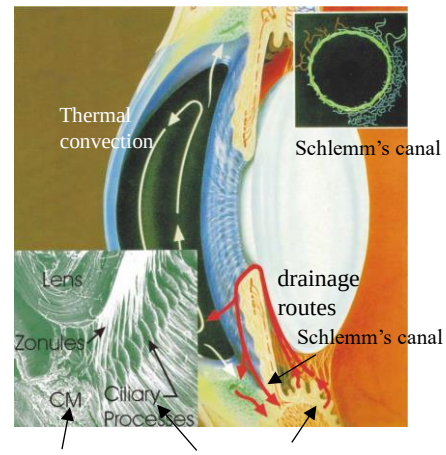
Aqueous humour

- Typical production rate of 2.4 µL/min (by ciliary body) – 1% of volume of anterior chamber per minute, peak in morning, minimum at night
- **Regulation** needed to maintain IOP – high IOP leads to glaucoma
- Two drainage routes, principal route at conjunction of iris, cornea and sclera – trabecular meshwork, and Schlemm's canal

Resistance of 3-4 mmHg/(µL/min)

Provided by:

1. Proteoglycan-rich gels in the trabecular meshwork **(interstitial flow)** $\frac{Q}{\Delta p} = \frac{\kappa A}{h}$
2. Endothelial lining of Schlemm's canal, bulging into the lumen of the canal **(channel flow)**



[Ethier et al]

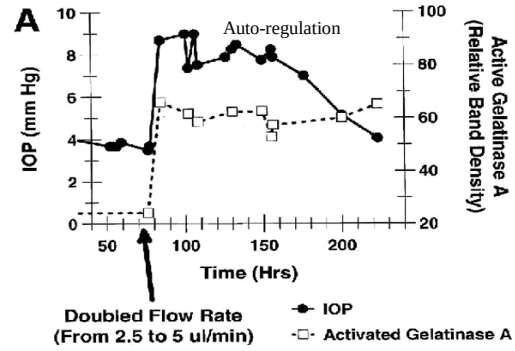
18

Aqueous humour liquid drainage: control of IOP

Provided by:

1. **proteoglycan-rich gels in the trabecular meshwork (interstitial flow)**
2. endothelial lining of Schlemm's canal, bulging into the lumen of the canal.

[Ethier, Barocas & Crawford Downs/Bradley et al

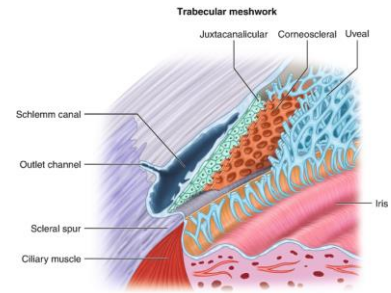


- High IOP implicated in glaucoma
- How could aqueous humour flow be controlled to regulate IOP?
- Experiments show an immediate increase in IOP with increased perfusion of media.
- IOP then returns to baseline after 150 hours.
- Perfusate collected from experiments contained increased gelatinase A (MMP-2).
- Suggests that ECM material is linked to control of IOP.

19

Aqueous humour liquid drainage: control of IOP

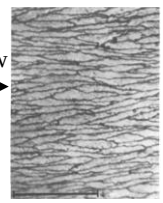
Provided by:
(i) proteoglycan-rich gels in the trabecular meshwork
(ii) endothelial lining of Schlemm's canal, bulging into the lumen of the canal. (channel flow)

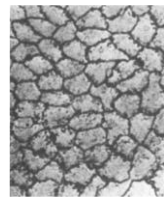


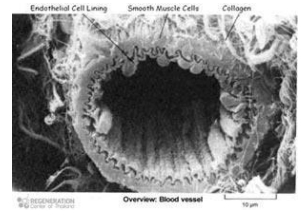
At stenosis/constriction in aorta (high WSS)

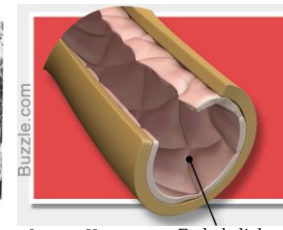
After stenosis (low WSS)

Flow









Endothelial cell lining

- Large arteries adjust their diameter over time (remodelling) in reaction to the wall shear stress (WSS). WSS sensed by endothelial cells lining the artery – mechanotransduction.

Difficult to study for Schlemm's canal… but we can do estimate

Source: https://link.springer.com/chapter/10.1007/978-981-15-5632-6_2

20

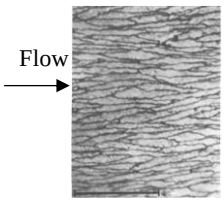
Aqueous humour liquid drainage: control of IOP

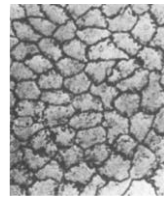
Provided by:
(i) proteoglycan-rich gels in the trabecular meshwork
(ii) endothelial lining of Schlemm's canal, bulging into the lumen of the canal.

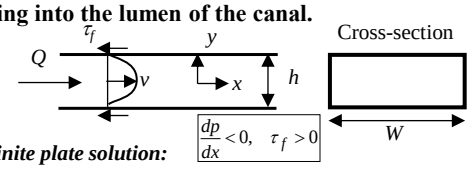
At stenosis/constriction in aorta (high WSS)

After stenosis (low WSS)

Flow







$\frac{dp}{dx} < 0, \quad \tau_f > 0$

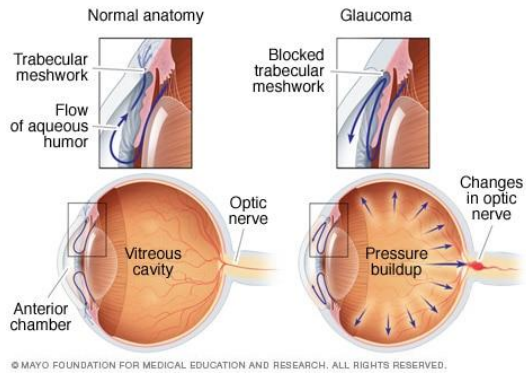
Use infinite plate solution:

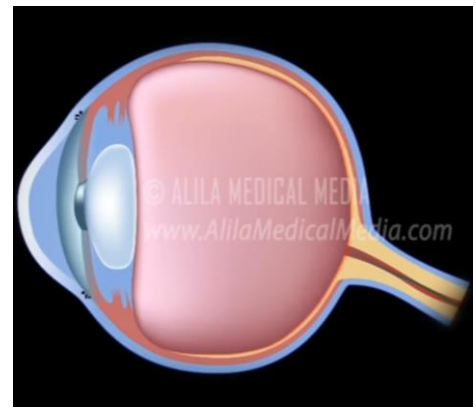
$$v_x = \left(\frac{1}{2\eta}\frac{dp}{dx}\right)\left(y^2 - \frac{h^2}{4}\right) \Rightarrow \tau_f = -\eta\frac{dv}{dy}_{y=h/2} = -\frac{h}{2}\frac{dp}{dx}$$

$$Q = 2W\int_0^{h/2} v_x dy = -\frac{Wh^3}{12\eta}\frac{dp}{dx} \qquad \Rightarrow \tau_f = \frac{6\eta Q}{Wh^2}$$

- Large arteries adjust their diameter over time (remodelling) in reaction to the wall shear stress (WSS). WSS sensed by endothelial cells lining the artery – mechanotransduction.
- Typical WSS in the range 2-20 dynes/cm^2 [1 dyne = 10^{-5} N, from CGS = cm–g –s units]
- Assume laminar Poiseuille flow, governed by viscous forces (Reynold's number is small as the vessels are so small). See 1B Fluids lectures. Take, e.g. Q = 0.24 μL/min, η = 7.5×10^{-4} Pa.s, W = 260 μm, h = 5 μm $\Rightarrow t_f$ = 2.7 dynes/cm^2
- Mechanism supported by preferential alignment of endothelial cells in Schlemm's canal.

How mechanics are indicated in disease: glaucoma

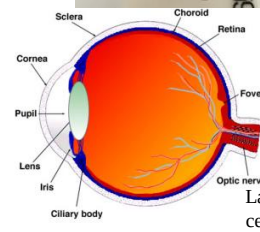




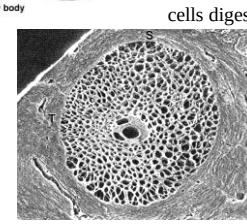
Source: https://www.youtube.com/watch?v=TgjdPgSxeYg;
https://www.centreforsight.com/treatments/glaucoma-treatments-migs/hydrus

Mechanics of Glaucoma:
IOP induced optic nerve head (ONH) damage

- Hypothesised that high IOP is implicated in damage to the ONH causing glaucoma.
- The **lamina cribrosa (LC)** is a porous connective tissue filling the ONH through which the nerve passes.
- ONH acts as a stress concentration in the sclera allowing exit of the optic nerve.
- Evidence suggests that damage to the ganglion nerve cells is associated with the LC.
- Can we model what are the factors controlling deformation of the LC?



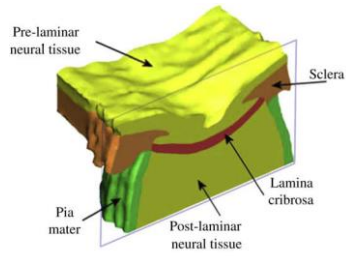
Lamina cribrosa, neural cells digested away



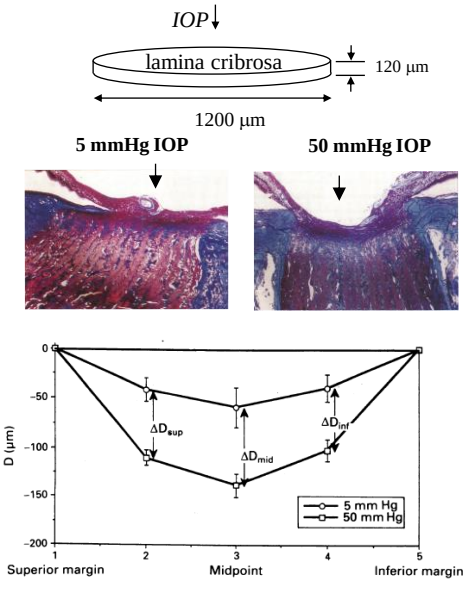
23

Mechanics of Glaucoma

- Significant deformation of LC due to IOP seen in experiments
- Models hampered by uncertainty in material properties.
- Results from finite element (FE) analysis highlight importance of scleral modulus.



Finite element model [Sigal and Ethier]

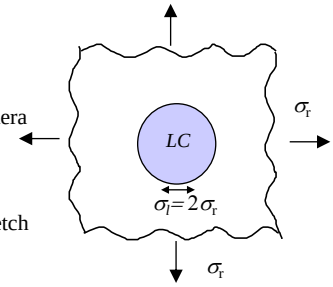


Deformation of LC (Yan)

24

Structural mechanics of the LC: Plane membrane model

- Strains of 5-8% can induce changes in neuronal cells. Can these strains arise in the LC?
- Assume that modulus of LC is much less than that of the sclera (c.f. foams, relative density $\rho^*/\rho_s = 0.1 \Rightarrow E^*/E_s = 10^{-3}$)
- Biaxial remote stresses. No radial stress at LC interface.
- Assume that the in-plane stretch of LC is determined by stretch of surrounding sclera



$$\varepsilon_l = \frac{\sigma_l}{E} = \frac{2\sigma_r}{E} = \frac{2\varepsilon_r}{(1-\nu)} \approx 4\varepsilon_r$$

subscripts
r = remote
l = local

Hence $\varepsilon_l \approx 1\%$ (see earlier calculation for ε_r) for **normal IOP**

Circumference of LC expands by 1%.

All strains in the LC are 1%.

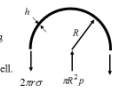
Not biologically damaging for normal IOP.

The eye as a pressurised shell

- Need to maintain shape to preserve optical properties.
- Shape maintained by internal pressurisation - intraocular pressure (IOP).
- Values of IOP (NB 1 mmHg = 133 Pa)
  - Normal = 15.5 mmHg
  - Changes with arterial pulse
  - Extreme = 50 mmHg
  - Loads due to accommodation (changing lens shape), blinking
  - Rubbing eyes, IOP ~80 mmHg.
- Overall structure can be represented as a thin-walled spherical shell.
- Wall properties given by sclera and cornea.
- Structural features at cornea and at optic nerve.
- Model as a sphere with no bending stresses to give biaxial stresses: $\frac{\sigma}{p} = \frac{R}{2h}$
- e.g. p =15.5 mmHg, h = 0.78 mm, R = 12 mm, E = 3 MPa

σ = 16 kPa $\varepsilon = \frac{\sigma}{E}(1-\nu) \approx \frac{\sigma}{2E}$ = 0.26%

Implications: change in eye size during different loads, failure?

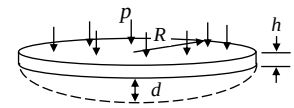


25

Structural mechanics of the LC: elastic plate

- Need to consider effects of:
  - In-plane membrane stress σ_m and bending stress σ_b
  - Boundary constraints (e.g. simply supported or clamped)
- Solutions for clamped edges: [Timoshenko, p412]

Circular uniformly loaded plate

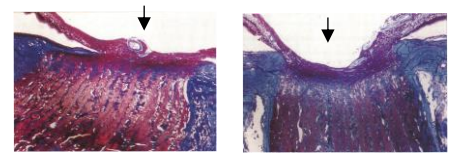


Central deflection $\frac{d}{h} + 1.85\left(\frac{d}{h}\right)^3 = 0.7\frac{p}{E}\left(\frac{R}{h}\right)^4$

Central (biaxial) stresses $\sigma_m = 0.91E\left(\frac{d}{R}\right)^2$, $\sigma_b = 1.78E\frac{dh}{R^2}$

- First term on LHS for small deformations (i.e. beam bending)
- Second term on LHS only for large deformations (i.e. cable/membrane)

5 mmHg IOP 50 mmHg IOP

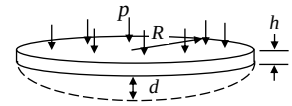


26

Structural mechanics of the LC: elastic plate

- Need to consider effects of:
  - In-plane membrane stress σ_m and bending stress σ_b
  - Boundary constraints (e.g. simply supported or clamped)
- Solutions for clamped edges: [Timoshenko, p412]

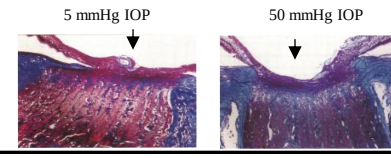
Circular uniformly loaded plate



Central deflection $\frac{d}{h}+1.85\left(\frac{d}{h}\right)^3=0.7\frac{p}{E}\left(\frac{R}{h}\right)^4$

Central (biaxial) stresses $\sigma_m=0.91E\left(\frac{d}{R}\right)^2$, $\sigma_b=1.78E\frac{dh}{R^2}$

- First term on LHS for small deformations (i.e. beam bending)
- Second term on LHS only for large deformations (i.e. cable/membrane)
- Taking data from Yan et al and Sigal et al: p = 50mmHg, R = 600μm, h = 120μm, d = 138 μm
- $\Rightarrow E$ = 0.73 MPa, σ_m = 27 kPa, σ_b = 60 kPa, $\varepsilon=\frac{\sigma(1-\nu)}{E}\approx\frac{\sigma}{2E}=6.0\%$
- Significant strains



27

Summary

	Structure	**Fluids in the eye**			
Define the context	Macro-anatomy of the eye	Blood flow in choroid	Transport through Bruch's membrane (interstitial fluid)	Aqueous humour drainage (two routes)	Glaucoma
When to apply Engineering & **How** to solve	The eye as a pressurised shell Ocular rigidity	"Starling resistor"	Poroelasticity *vs.* diffusion	Mechano-biology	Membrane model; Elastic plate model
What is the broader impact	IOP as diagnostic marker Tonometry	Flow autoregulation	Drug delivery strategy	Flow autoregulation for IOP control	Mechanical damage to optic nerve head

28

References

C Boote, S Hayes, M Abahussin KM Meek. Mapping Collagen Organization in the Human Cornea: Left and Right Eyes Are Structurally Distinct. Investigative Ophthalmology & Visual Science, March 2006, Vol. 47, No. 3

Y Komai T Ushikif, The Three-Dimensional Organization of Collagen Fibrils in the Human Cornea and Sclera. Invest Ophthalmol Vis Sci 32:2244-2258,1991

A Elsheikh and K Anderson. Comparative study of corneal strip extensometry and inflation tests. J. R. Soc. Interface 2005 2, 177-185

K Anderson, A El-Sheikh T Newson. Application of structural analysis to the mechanical behaviour of the cornea. J. R. Soc. Interface 2004 1, 3-15

HK Graham, DF Holmes, RB Watson, KE Kadler. Identification of Collagen Fibril Fusion during Vertebrate Tendon Morphogenesis. The Process Relies on Unipolar Fibrils and is Regulated by Collagen-proteoglycan Interaction J. Mol. Biol. (2000) 295, 891-902

Sigal et al, Finite element modeling of optic nerve head biomechanics, Investigative ophthalmology and visual science, 2004, 45, 4378-4387

Myers et al. The inflation response of the posterior bovine sclera, Acta Biomaterialia 6 (2010)4327-4335 and also presentation, March 2011

MJ Stafford. The histology and biology of the lens. Bausch & Lomb, 2001. Downloaded on 3/5/11 from http://www.optometry.co.uk/uploads/articles/0b3e55d71662f4e8381aea8637c48f4f_stafford20010112.pdf

References

Introductory biomechanics: from cells to organisms. CR Ethier and CA Simmons, 2007 CUP

Sigal et al, Finite element modeling of optic nerve head biomechanics, Investigative ophthalmology and visual science, 2004, 45, 4378-4387

Yan et al, Deformation of the lamina cribrosa by elevated intraocular pressure. British J of Ophthal, 1994, 78, 643-648

Timoshenko and Woinowsky-Krieger. Theory of plates and shells, 2nd Edition, McGraw-Hill, 1959

Myers et al. The inflation response of the posterior bovine sclera, Acta Biomaterialia 6 (2010)4327-4335 and also presentation, March 2011

CR Ethier et al. Ocular biomechanics and biotransport. Annual Rev. Biomed Eng. 2004, 6:249-273

CR Ethier, VH Baracas, J Crawford Downs. Ocular biomechanics in Glaucoma. Ophthamology Research: Mechanics of Glaucoma, Edited by J Tombran-Tink, CJ Barnstable. MB Shields, Humana Press, Totowa NI

Pallikaris et al, Ocular rigidity in living human eyes, Investigative ophthalmology and visual science, 2005, 46,409-414

Pallikaris et al, Ocular rigidity in patients with age-related macular degeneration, American J Ophthal, 2006, 141,611

MJ Levesque, D Liepsch, S Moravec and RM Nerem. Correlation of endothelial cell shape and wall shear stress in a stenosed dog aorta, Arterioscler Thromb Vasc Biol 1986;6;220-229

CR Ethier, AT Read, D Chan. Biomechanics of Schlemm's Canal Endothelial Cells: Influence on F-Actin Architecture. Biophysical Journal Volume 87, 2004; 2828–2837

IA Sigal, CR Ethier. Biomechanics of the optic nerve head. Experimental eye research 88 (2009) 799-807