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
   - 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

↓

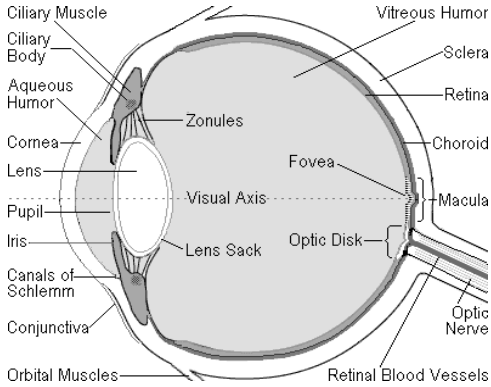
When to apply Engineering & **How** to solve

↓

What is the broader impact

Normal Eye Anatomy: Material/Structure to Function (Focusing)

For clear vision: light rays travel through the front layers of the eye (the cornea and lens). The cornea and lens bend the light ray so it lands on the retina at the back layer of the eye. The retina then sends a signal to the brain for vision formation.



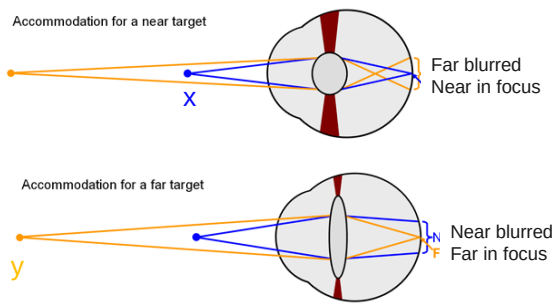
The cornea contributes the majority (2/3) of the eye's focusing power but is fixed focus.

The (crystalline) lens sits behind the iris and contributes the remainder (1/3) of the eye's focusing power.

The focal distance of the eye is altered by changing the shape of the lens via the action of the ciliary muscles.

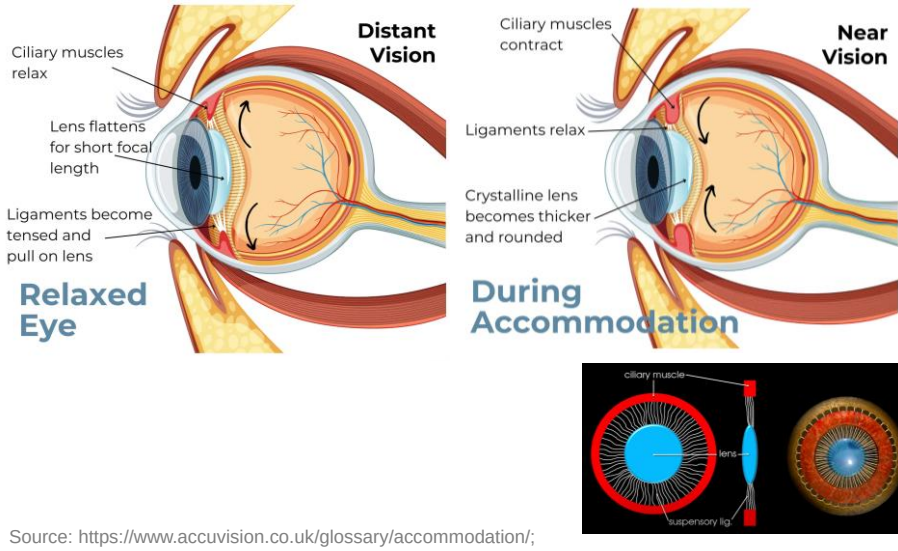
Lens Accommodation

- The transparent biconvex lens structure changes shape to change focus.
- Lens curvature is controlled by ciliary muscles
  - By changing curvature, the eye focuses on objects at different distances.
  - This process is called accommodation.
- The 'amplitude of accommodation (A)' is the maximum potential increase in optical power that an eye can achieve in adjusting its focus. It refers to a certain range of object distances for which the retinal image is as sharply focussed as possible.
- Optical power: $P = 1/f$ (f,= focal length, unit meter (m); P unit = dpt, or m^{-1})



$A = P_x - P_y$

Lens Accommodation

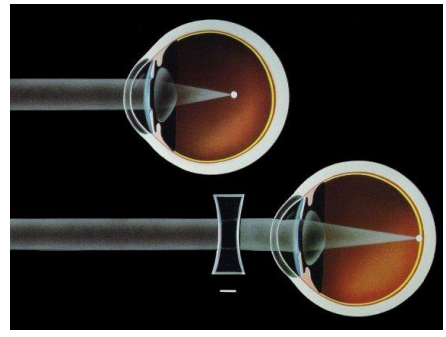


Source: https://www.accuvision.co.uk/glossary/accommodation/; https://www.youtube.com/watch?v=7lBtlGvS1Gc

Myopia

Myopia = Nearsightedness: an inability to view distant objects in focus

The shape of eye prevents light from bending properly, so that light is aimed in front of the retina.
For example, the cornea at the front of the eye may be too steeply curved, or the eye may be longer front to back than normal.

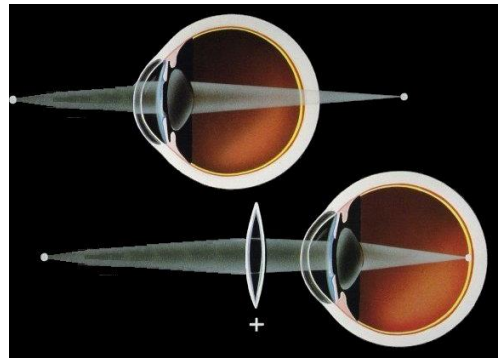


Corrected by a concave lens

Hyperopia

Hyperopia and Presbyopia = farsightedness, an inability to view close-up objects in focus.

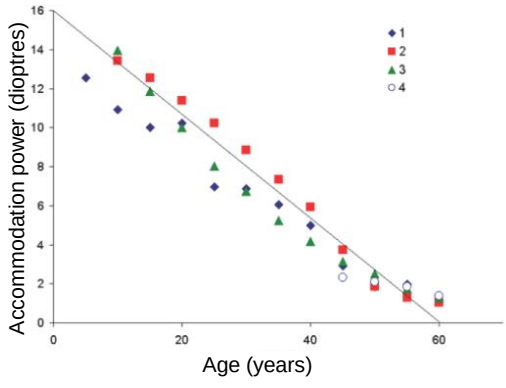
The shape of the eye prevents light from bending properly, so that light is aimed behind the retina. For example, the eye may be shorter than normal (from front to back) or the cornea at the front of the eye may be too flat.

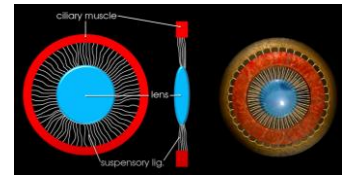


Corrected by a convex lens

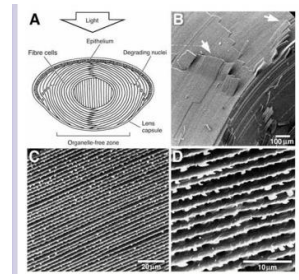
Presbyopia

- Presbyopia develops when the eye's lens loses its natural flexibility
- Presbyopia, or "old man's eyes," affects almost all people by the age of 50.
  - Loss of accommodative ability, where near field focusing becomes impossible





'Material' problem



Mechanical Testing of Lens

Lens as a 'passive' material with linear elastic property

- Indentation testing of lens across the surface
- Test 8 points across lens
- Three rows when possible
- 1mm spacing
- Calculate shear modulus, G (Pa), from:

$$P = \frac{4RdG}{1-\upsilon}$$

where:

P = total load (N)

R = indenter radius (m)

d = maximal depth of penetration (m)

υ = Poisson's ratio

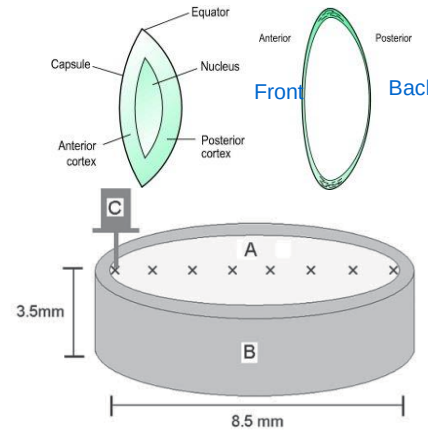


Figure 2. A schematic diagram showing the method used for measurement of lens stiffness. The equatorial section of a lens (**A**), obtained as illustrated in Figure 1, was held in a metal ring (**B**) and the lens section was moved across and underneath the DMA probe (**C**) in 1 mm steps (see Figure 1). At each point a measurement of stiffness was made.

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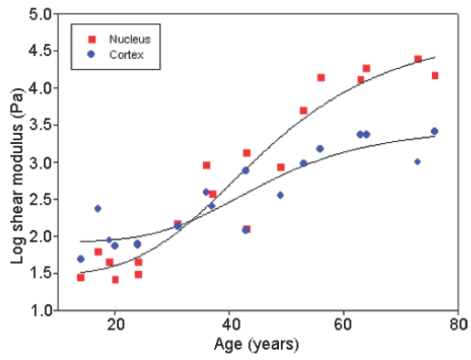
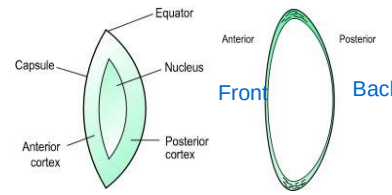
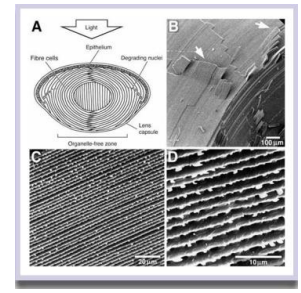
Lens changes with age







- Nucleus and cortex of lens becomes stiffer with age, note orders of magnitude change
- The lens also becomes larger
- Lens stiffening over age: harder to deform and focus

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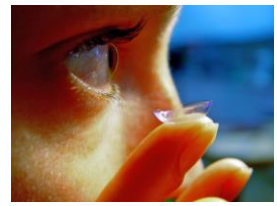
Functional repair strategy for short-sightedness (Myopia)

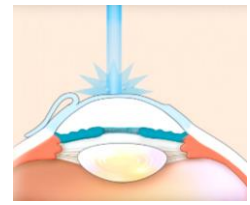
Problem: Myopia: the shape of eye prevents light from bending properly, so that light is aimed in front of the retina.

Engineering solution:

https://en.wikipedia.org/wiki/Glasses



https://en.wikipedia.org/wiki/Contact_lens#/media/File:Contact_Lens_Ayala.jpg



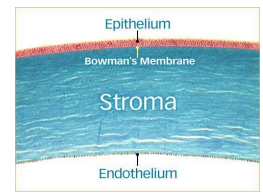
https://www.fda.gov/medical-devices/surgery-devices/lasik

Each strategy is associated with a different tissue/ implant interaction criteria, and management for outcomes.

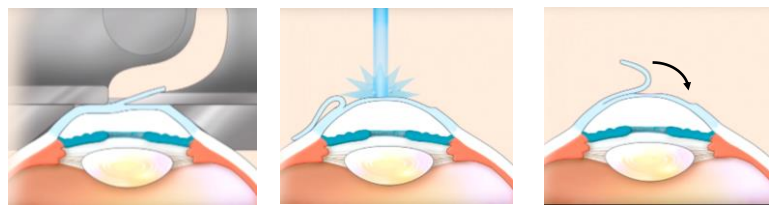
Myopia: LASIK Surgery

LASIK = Laser-Assisted *In Situ* Keratomileusis

Recall that 2/3 of the eye's focussing power comes via the cornea. LASIK is used to re-shape the cornea to restore vision.



- The cornea is opened in a "flap" to expose the stroma
- A laser is used to vaporize regions of the corneal stroma
- The flap is closed and naturally re-adheres (no sutures are required)



https://www.fda.gov/medical-devices/surgery-devices/lasik

Myopia: Contact Lenses

- History of contact lenses dominated by materials and fabrication developments.
- Leonardo da Vinci (1508) described altering corneal power by immersing the eye in a bowl of water.
- First published contact lens use by Fick (1888).
- Early lenses of glass, PMMA introduced in 1936.
- Corneal lenses first demonstrated in 1948.
- Silicone rubber ‘soft lens’ in 1965; poor results due to hydrophobic surface.
- Wichterle (1961) produced prototype soft lens from hydrophilic gel, patent acquired by Bausch & Lomb.
- Rigid PMMA lenses hampered by lack of gas permeability. Developments e.g using silicone acrylates have been successful.
- Johnson & Johnson purchased and overhauled moulding process to give low cost disposable lenses.
- Developments concerned with infection and compliance.

Adolf Fick

Otto Wichterle

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Contact Lenses

Types of lenses (Elastic modulus):

- Glass 1880s-1930s (70 GPa)
- PMMA 1930s-80s (4 GPa)
- Silicone acrylates (gas permeable) 1980s-90s (~GPa)
- Silicone rubbers 1960s (1-10 MPa)
- Hydrogels 1970s-present (kPa-MPa)

Cornea elastic modulus: 1-15 MPa (depending on location and orientation)

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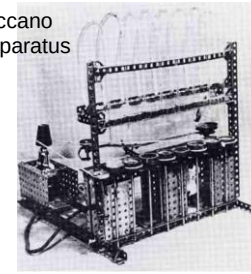
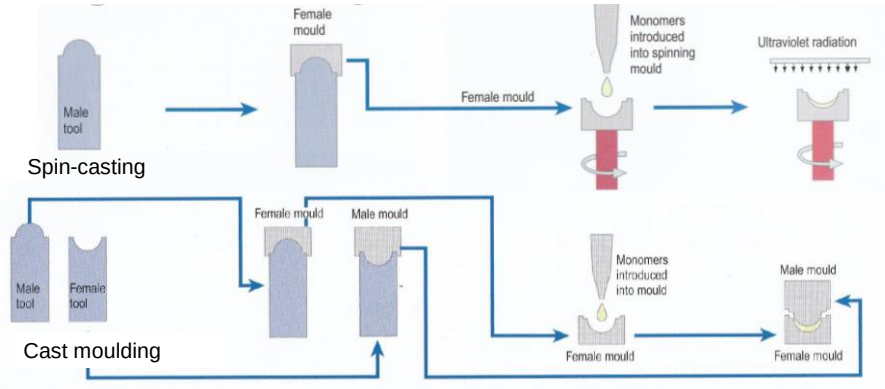
Lens manufacture

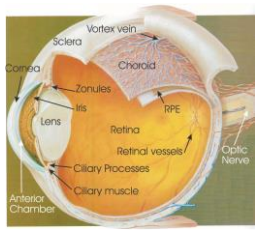
Wichterle's Meccano spin-casting apparatus



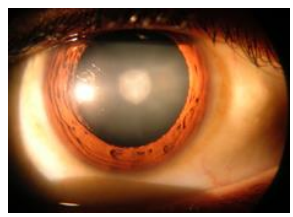
- Wichterle's original spin casting process still in use.
- Cast moulding is the dominant manufacturing process.
- Manufacture, packaging and sterilization important.

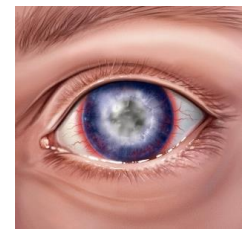


Disease



Disease symptom: Lost of sight





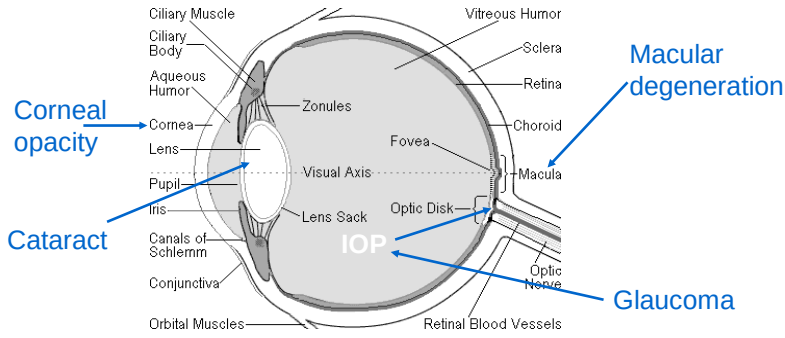
A cataract is defined as a cloudy (opaque) lens. This is extremely common in the elderly. The leading cause of blindness (almost half cases).

Glaucoma is associated with excess IOP causing damage to the optic nerve. Second most common form of blindness.

Corneal opacity is a cloudy (opaque) cornea. This is most often (but not exclusively) due to injury, inflammation or infection, and thus sudden in onset compared with the gradual deterioration of the lens in cataracts.

Repair solutions for disease

1. Define the ***normal function*** of the relevant body systems
2. To understand the ***disease processes*** that have impaired the normal body function being replaced
3. **When** to apply Engineering (can the functions be replaced by engineering alone?) → **solution**



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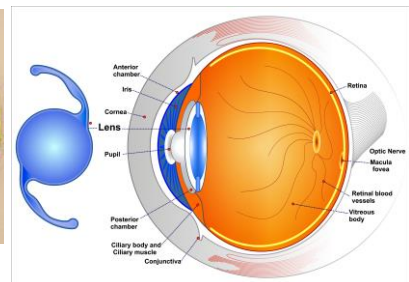
Cataract: Cataract Surgery & Intraocular Lens

- Cataracts are an enormous problem in the developing world: it is estimated that 35 million more operations could take place a year compared with the 10 million currently
- Artificial intraocular lenses (IOLs) are implanted after removal of the cloudy lens (cataract) in a very common surgery (10,000,000 IOLs implanted per year)
- Although first done in 1950 (St Thomas hospital), the procedure gained significant popularity in the 1970s with improved IOL materials.



https://seeclearkalamazoo.com/services/cataracts/intraocular-lens-options/

https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/ACIOL/index.htm

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Cataract: Intraocular Lens Materials

- Early intraocular lenses were PMMA (*E* ~ 3 GPa).
- Modern acrylate lenses are flexible so as to be folded for the surgical insertion; these include both hydrophobic and hydrogel (hydrophilic) polymers.
- In addition to acrylates silicone rubber has been used (*E* ~ 4 MPa).
- Modern lenses are significantly lighter as well, 20 mg on average compared with 110 mg for early PMMA lenses.
- The reduction in stiffness associated with the modern, flexible lenses allowed for a change in surgical procedure for a minimally-invasive approach requiring no stitches
  - Recovery is much faster
  - Outcomes are significantly approved.
- IOL materials are often doped with UV absorbing additives to protect the retina from radiation damage.

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Cataract: Cataract Surgery & Intraocular Lens

Video: http://catalog.nucleusinc.com/generateexhibit.php?ID=34722&ExhibitKeywordsRaw=

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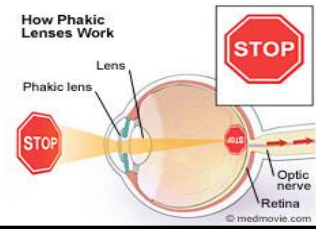
Intraocular Lens Future

- Historically IOLs are monofocal—accommodation is lost
- Multi-focal and accommodating IOLs are currently under development for improving on monofocal IOLs
  - A word of caution is warranted here: in many types of medical implants, the earliest designs and simplest principles have proven more effective than "advanced" designs.
- In the future, advanced IOLs may be used to correct vision defects, instead of contacts, glasses and laser surgery.
  - "Phakic" IOLs are like permanent contact lenses implanted between the cornea and iris.



https://www.fda.gov/medical-devices/phakic-intraocular-lenses/what-are-phakic-lenses

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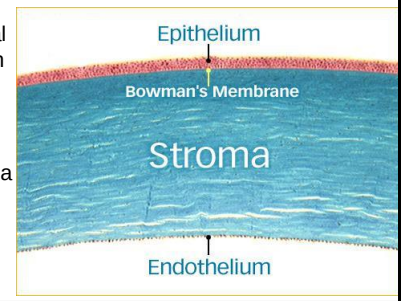
Corneal Opacity: Corneal Transplants

- In cases of corneal opacity, transplants from donor eyes are very successful
  - However, as with all transplant surgeries, there is a risk of rejection
  - There is also a significant shortage of donor corneas, waiting lists are up to two years and likely to increase significantly since eyes with laser surgery are unusable as donors.
- There have been some precedents of using polymeric materials (PMMA, in particular) for corneal transplants, especially in cases of a failed cornea transplant.
  - Complications include induced glaucoma, extrusion of the implant, and inflammatory reactions
  - These tend to be very invasive procedures, not just involving the cornea itself but invading the globe substantially.
- Hence aim to develop a material to act as the corneal stroma, to allow for re-creating the cell layers on both surfaces to better mimic a real cornea.
- It would be a bonus if the material would "heal" into the surrounding healthy tissue.
- Current status is that corneal tissue engineering has a long way to go - but is being actively pursued.



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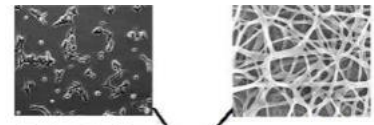
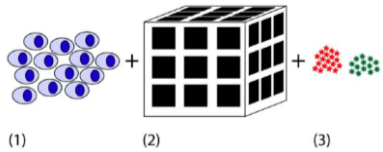
Corneal Tissue Engineering

General theme: instead of replacing defective tissue with man-made devices, try to re-grow healthy tissues by making living implants with active cells.



Isolated cells

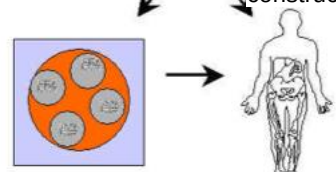
Biodegradable polymer scaffold



(1) cells + (2) biomaterial scaffolds + (3) growth factors and chemical signals

Cells seeded onto scaffold. As cells produce ECM and proliferate, scaffold degrades

Implant the cell-scaffold construct directly

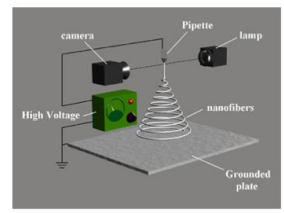


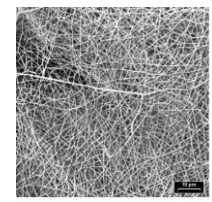
Grow tissue in vitro in a bioreactor prior to implantation

Corneal Tissue Engineering

- Key properties of scaffold:
  - composition
  - cytocompatibility
  - porosity
  - permeability
  - stability/resorption rate
  - ease of manufacture
  - mechanical properties (stiffness and strength)

http://nano.mtu.edu/Electrospinning_start.html





- Scaffold materials
  - naturally derived (e.g. collagen)
  - polymeric (e.g. biodegradeable PLGA)
  - apatite (bone, tooth replacement)
  - hydrogels

- Current challenges for man-made stroma matrices include poor mechanical properties and poor optical transparency.

Glaucoma: Aqueous humour regulation and IOP

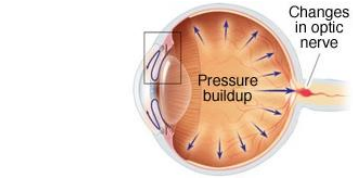
- Typical production rate of 2.4 μL/min – 1% of volume of anterior chamber per minute, peak in morning, minimum at night
- **Regulation** needed to maintain IOP – high IOP leads to glaucoma

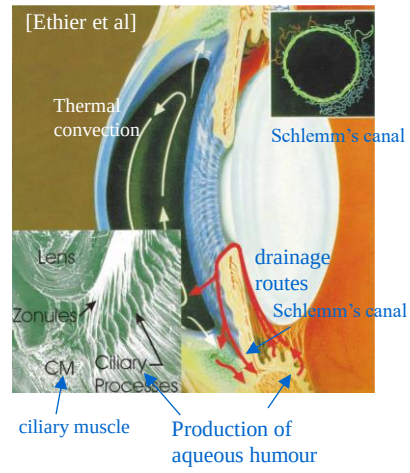
- Two drainage routes, principal route at conjunction of iris, cornea and sclera – trabecular meshwork, and Schlemm's canal

Resistance of 3-4 mmHg/μL/min

Provided by:

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



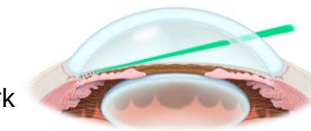


Glaucoma: Treatment Options

Eyedrops (non-invasive): all work by reducing the pressure in eyes, e.g. increased tissue permeability

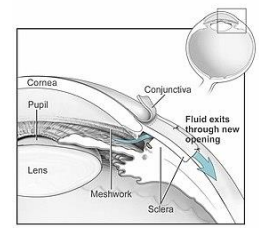
Laser treatment:

- laser trabeculoplasty – a laser to open the drainage tubes within the trabecular meshwork which allows more fluid to drain out;
- cyclodiode laser treatment – a to destroy some of the eye tissue that produces the liquid



Surgery

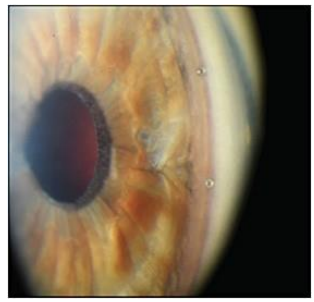
- trabeculectomy (most common), to remove part of the eye's trabecular meshwork and adjacent structures.



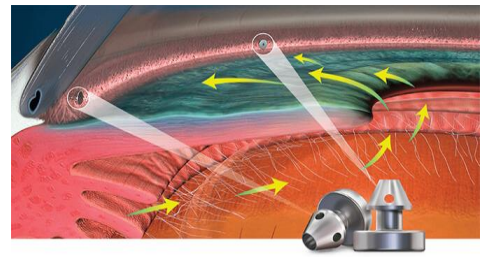
Source: https://ocvermont.com/glaucoma/selective-laser-trabeculoplasty/; https://en.wikipedia.org/wiki/Trabeculectomy

Glaucoma: Treatment Options via Engineering Devices

Minimally invasive



iStent inject ® (Titanian; by-pass)



XEN® Gel (Gelatin; by-pass)

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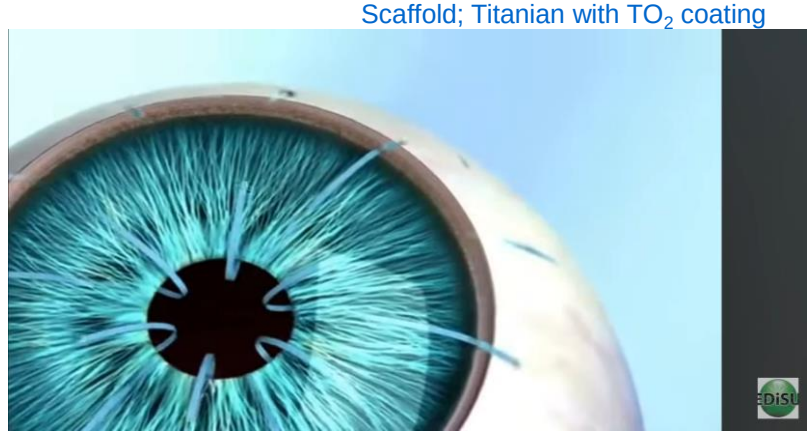
Glaucoma: Treatment Options via Engineering Devices

Minimally invasive

Hydrus™

Scaffold; Titanian with TO_2 coating



Source: https://www.centreforsight.com/treatments/glaucoma-treatments-migs/hydrus

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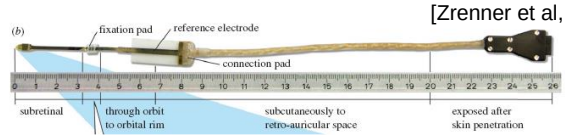
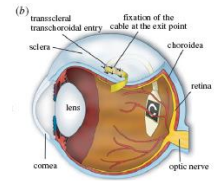
Macular degeneration: Subretinal chips

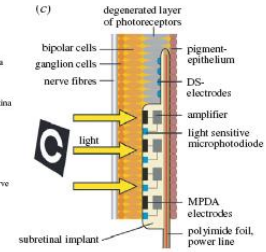
[Zrenner et al, 2010]



- Macular degeneration/ retinitis pigmentosa affect 15 million people worldwide.
- Where the inner retina survives, replace photoreceptors by electronic circuits that directly stimulate the retinal nerve cells.
- Team project: surgeons, medics, scientists, engineers, industrialists…
- Progressive advance, include in vitro trials, animal studies, account for biostability, surgical feasibility, safety.

- Design adopted had following features:
  - 1500 pixel microphotodiode array
  - CMOS chip on polyimide foil substrate
  - one amplifer per pixel
  - silicone cable connection
  - wirelessly operated power/ control unit.





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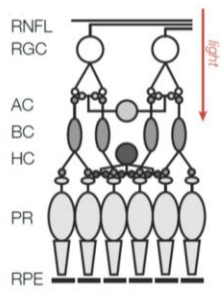

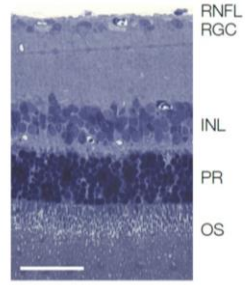

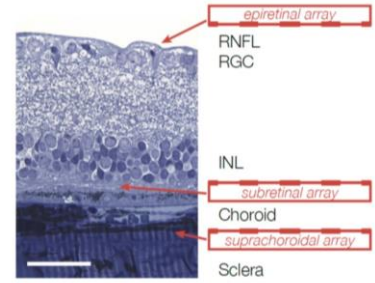

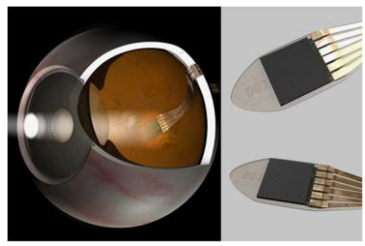

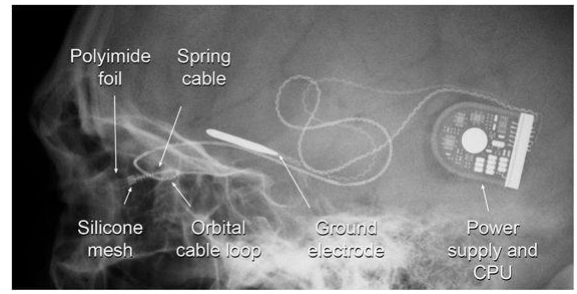

https://www.nature.com/articles/eye2016280
https://en.wikipedia.org/wiki/Retinal_implant

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Summary: Repair solutions for disorder &disease

1. Define the ***normal function*** of the relevant body systems
2. To understand the ***disorder*** or ***disease processes*** that have impaired the normal body function
3. **When** to apply Engineering (can the functions be replaced by engineering alone?) → **solution for <u>functional replacement</u>**