Never Stand Still

BIOM1010: Excitable tissue, neural interfaces and bionic eyes

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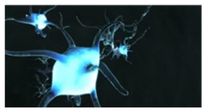
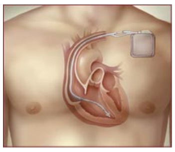
Lecture overview



- What is neural engineering?
- Basic neurophysiology
  – Structure of a neuron
  – Action potentials
  – Cardiac action potentials and the electrocardiogram
- Neural interfacing and neuroprosthesis
  – Physiology of the eye and retina
  – How a retinal prosthesis (bionic eye) works
  – Bionic eye developments at UNSW
- Future directions in neural engineering

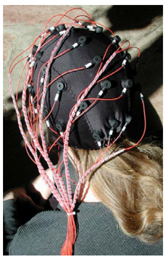
What can we do with some wires and a body?

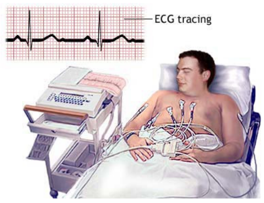
- We can stimulate, cut and image



What can we do with some wires and a body?

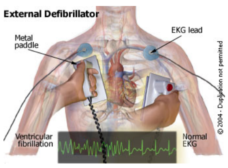
- We can record



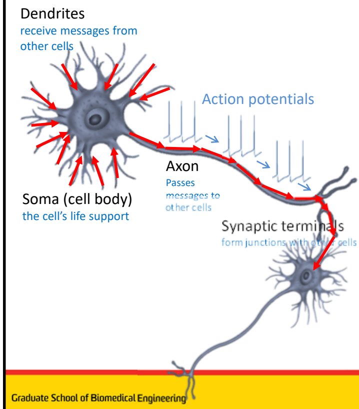


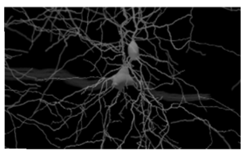
What can we do with some wires and a body?

- We can really have some fun and do both at once

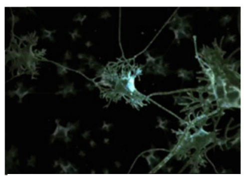


Structure of a neuron





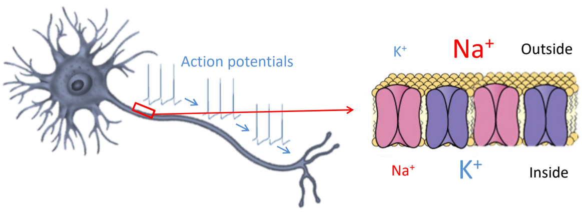
Neurons are electrically excitable



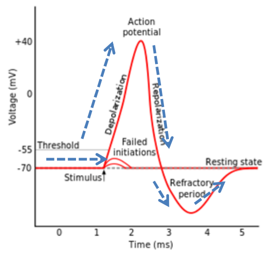
Neurons communicate with each other through their dendrites and axon

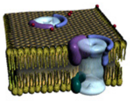
What is an action potential ?

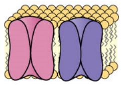
- An action potential (also known as a nerve impulse or spike) is a pulse-like wave of voltage that travels along excitable cell membranes



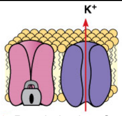
What is an action potential ?



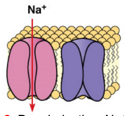




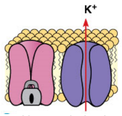
1. Resting state: voltage-gated Na+ channels closed. K+ channels partly open (leaky).



3. Repolarisation: Once the cell reaches its peak positive potential, Na+ channels are inactivated and K+ channels open. The cell repolarises to a negative membrane



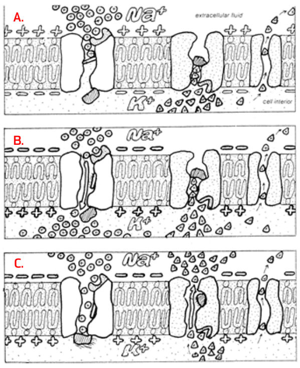
2. Depolarisation: Na+ channels open. An action potential begins when the neuron is depolarised to its threshold potential.



4. Hyperpolarisation: K+ channels remain open and Na+ channels inactivated. The membrane potential becomes more negative than the resting potential

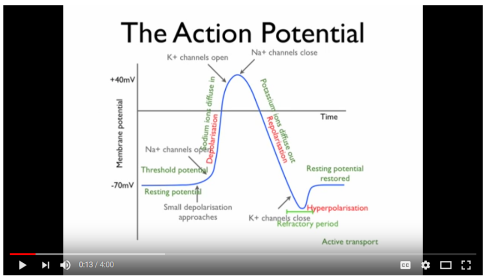
Ion channels

- Cell membrane comprise a phospholipid bilayer with each lipid having a hydrophobic and hydrophilic region
- Contain separate channels for different ions
- Many channels contain voltage sensitive 'gates'
- Na+ channel also has a time dependent inactivation gate
- A. Normal resting potential: leaky K+ channel
- B. Depolarisation: fast Na+ gate opens
- C. Repolarisation: slow Na+ gate closes and a slow K+ gate opens



Action potential explained

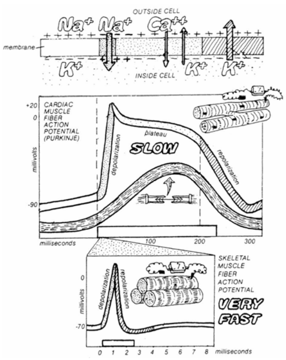
https://youtu.be/7EyhsOewnH4



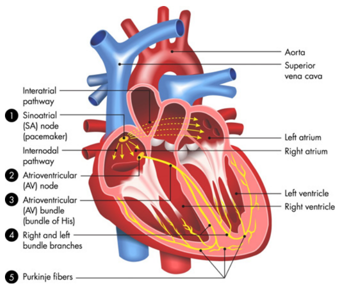
The Action Potential

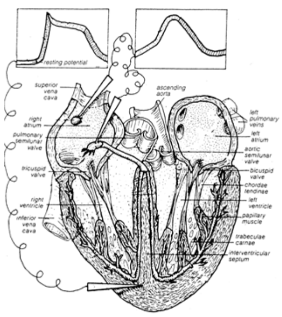
Cardiac muscle

- Duration of cardiac action potential can be 100 times more prolonged than that of skeletal muscle or nerve impulse
- Long refractory period
- Plateau sustained by slow Ca^{++} entry and slow K^{+} efflux

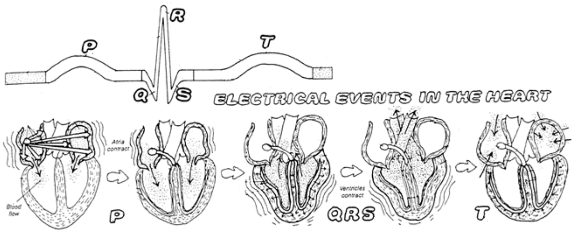


Anatomy and conduction



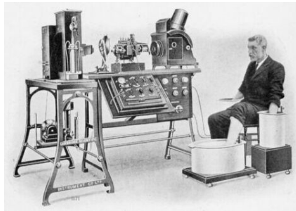


The electrocardiogram (ECG)



Physiological measurements

- While the technology has advanced the premise of biopotential recording remains



ECG recording

Early Clinical Telehealth Trials

- 85% of health care spend on chronic disease (trillions of $ globally)

A phospholipid molecule:

a) Can form mucous cells to capture fat fragments

b) Can aggregate into a lipid bilayer to form a hydrocele

c) Has a hydrophobic end that is comprised of a fatty acid chain

d) Has a hydrophobic tail and a hypophalic head

With regards ion channels:

a) Potassium channels have time and voltage dependent gates

b) Membrane depolarisation is principally caused by potassium influx

c) Sodium channels can be characterised as having an activation and an inactivation gating variable

d) During membrane repolarisation the sodium channels are activated by the membrane voltage reaching threshold

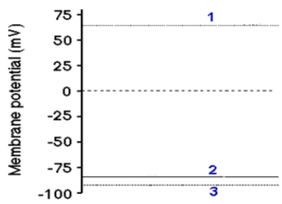
At a resting state, the three numbers on the figure could represent cell potentials in the following way:

a) $1 = E_{Cl}$, $2 = V_m$, $3 = E_K$

b) $1 = E_{Na}$, $2 = E_K$, $3 = V_m$

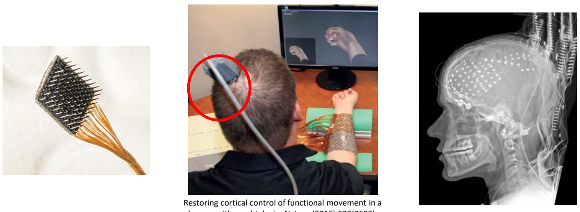
c) $1 = V_m$, $2 = E_{Cl}$, $3 = E_{Na}$

d) $1 = E_{Na}$, $2 = V_m$, $3 = E_K$



The Interfacing Grand Challenge

$20 billion global market, 15% growth, half a million patients



Restoring cortical control of functional movement in a human with quadriplegia, Nature (2016) 533(7602).

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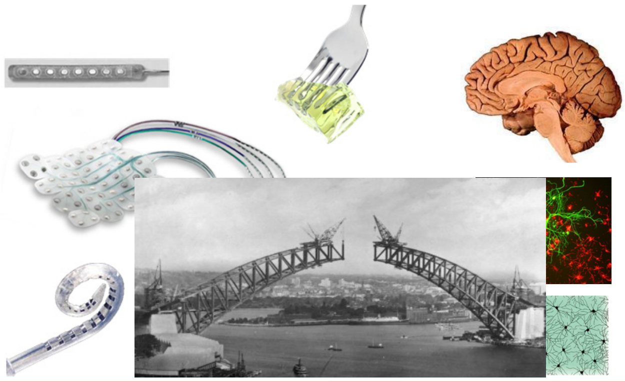
The Interfacing Grand Challenge



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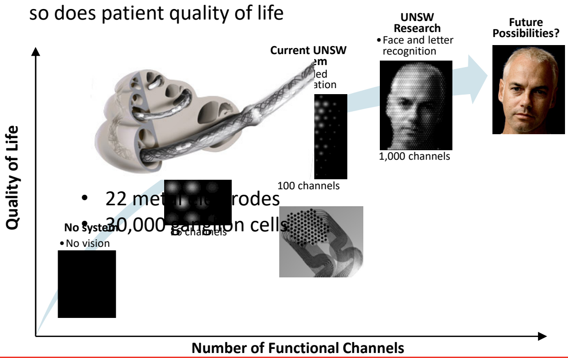
Why is the interface so critical?

- As number of functional channels increase, so does patient quality of life



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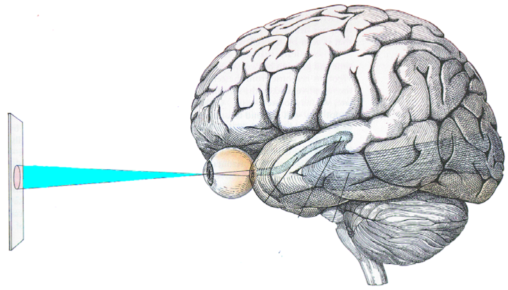
The Human Visual Pathway



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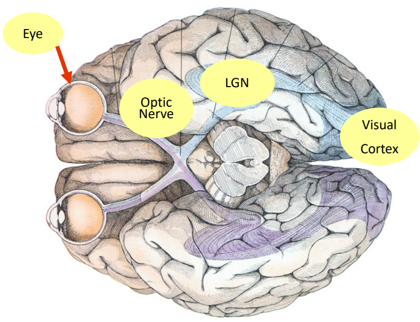
The Human Visual Pathway



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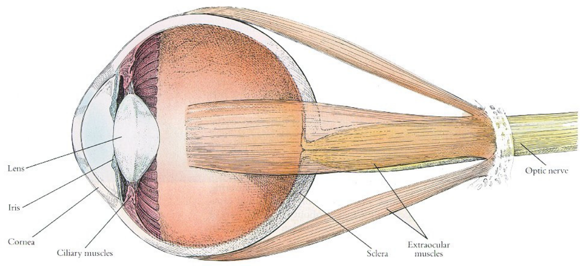
The function of the non-retinal components of the ocular anatomy is to maintain a focused, clear image of visual stimuli fixed on the surface of the retina



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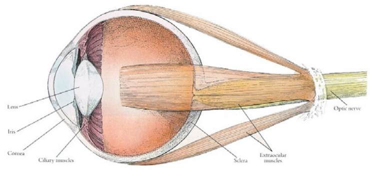
Sclera and cornea (tunic I)

- Sclera maintains form of the globe
- Anterior surface covered by conjunctiva
- Cornea is non-vascular and is continuous with sclera
- Cornea forms 15% of globe anterior

Choroid, ciliary body and iris (tunic II)

- Choroid 85% of globe posterior
- Choroid loosely connected externally to the sclera and internally to retina
- Ciliary body produces aqueous humour and adjusts eye to focus on near objects



Retina (tunic III)

- Forms interior surface of eye from fovea centralis to ora serrata near ciliary body
- Consists of ten layers between choroid (outer surface) and vitreous humour (inner surface)

Cornea

- Light enters eye at anterior surface of cornea
- Acts in much the same way as the lens of a photographic camera
- Approximately two-thirds of the bending of light necessary for providing focus takes place at the air-cornea interface

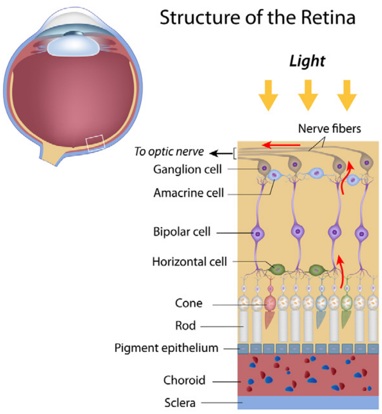
Lens

- Provides light bending power in addition to the cornea
- Primary role is distance compensation required to maintain focus on the retinal surface
- Anterior surface changes shape, more spherical for near objects, flatter for far ones, by contraction or relaxation of the ciliary muscles

Iris

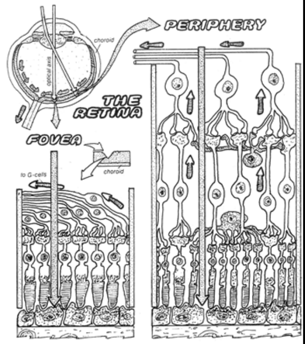
- Circular curtain suspended within aqueous humour immediately behind cornea
- Adjusts amount of light on retina
- Pupil is at centre of iris
- Changes size with contraction of iris

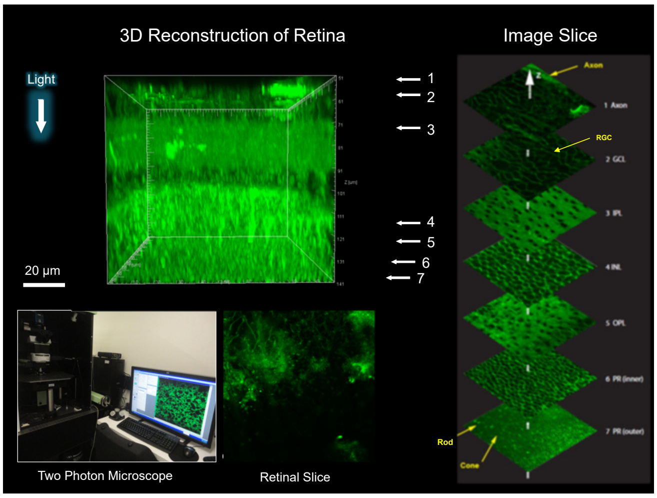
The Retina



Retinal layers

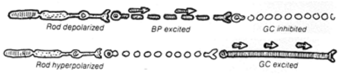
- Bipolar (BP) cells transmit signals from photoreceptors (rods and cones) to ganglion cells (GC)
- Horizontal and amacrine cells have no axons, performing inhibitory functions
- Interact at the photoreceptor and ganglion cell layer respectively
- Nearly 1:1 correspondence between cones and GC in fovea, 100:1 between rods and GC in periphery





Photoreceptor excitation

- Rods contain light sensitive rhodopsin (R)
- In the dark, R is stable signaling Na^+ channels to stay open, depolarising rods and their synapses. This activates the inhibitory BP cells thus inhibiting the ganglion cells.
- In light, decomposition of R signals the Na^+ channels to close, thus hyperpolarising rods and their synapses. This leads to inhibition of BP cells and the excitation of the ganglion cells.



Select the statement that is NOT correct with regard to the structure of the eye:

a) The iris regulates the amount of light entering the eye

b) The eye's refractive media comprise the cornea and lens

c) The ciliary muscles are used to focus the image on the retina by moving the lens backwards and forwards

d) Comprises an outer tunic of the cornea and sclera

The retinal ganglion cell layer:

a) Is at the front (anterior) of the retina

b) Contains dendrites that collect at the optic disk

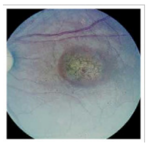
c) Consists of rods and other photoreceptors

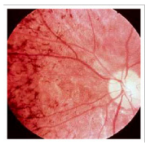
d) Synapses directly with the photoreceptors

The intermediate cell layer:

a) Consists of bipolar, horizontal and amacrine cells
b) Is at the anterior of the retina
c) Passes signals from the pigment epithelium to the ganglion cells
d) Requires a one-to-one correspondence between photoreceptor and ganglion cell

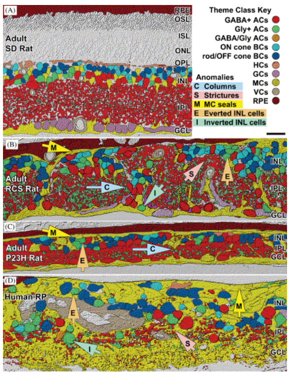
The problem

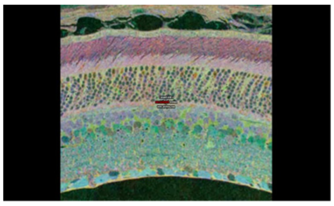

Age-related Macular Degeneration (AMD)


Retinitis Pigmentosa (RP)

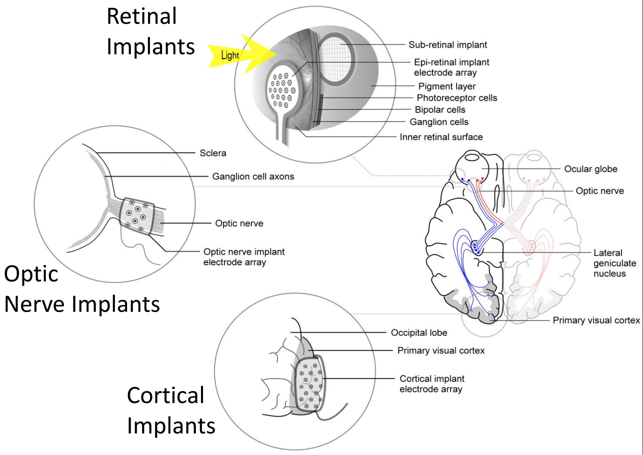
- Together, AMD and RP affect at least 30 million people in the world
- They are the most common causes of untreatable blindness in developed countries (RP affects 1 in 3500 in USA)
- There is no effective means of restoring vision
- Multi-billion $ market

Retinal remodelling



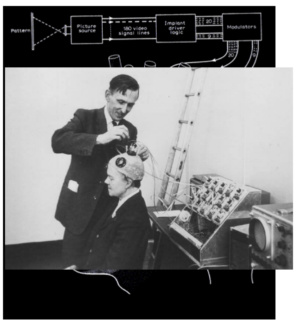


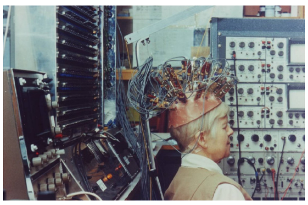
Marc et al, Prog Retinal and Eye Res, 22, 2003

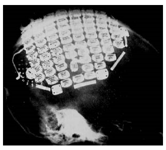


Early Interfaces

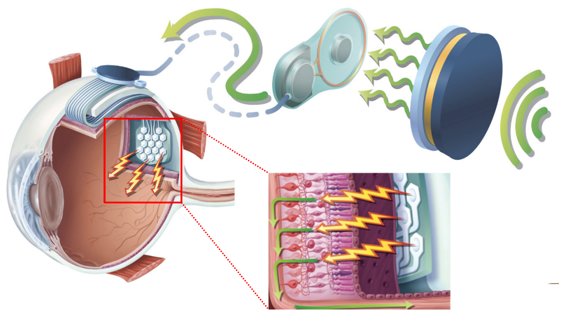
Giles Brindley's Visual Prosthesis ca 1968



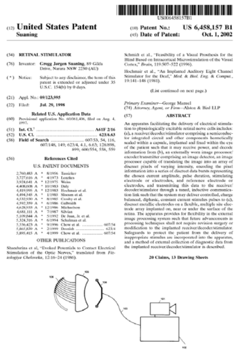


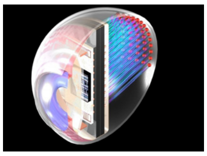


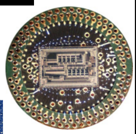
How Does Our Bionic Eye Work?

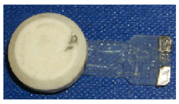


The Plan - Human Implants by 2000









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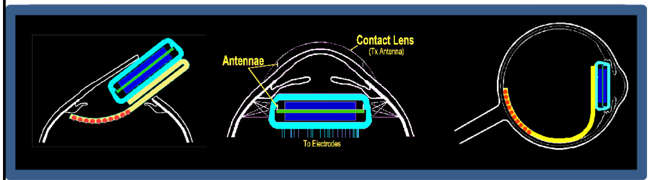
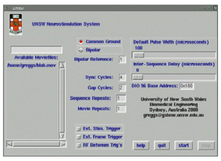
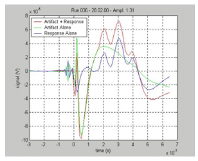
The Reality - Sheep Implants by 2000







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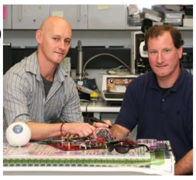
The Early Years (2001-2008)

- Dr Yves Kerdraon (now an ophthalmologist at Sydney University)
- Dr Luke Hallum (now at New York University)
- Phil Preston (UNSW)
- Dr Spencer Chen (now at University of Texas, Austin)
- Prof John Morley (now at the Western Sydney University)
- A/Prof Torsten Lehmann (UNSW)
- Dr Yan Wong (now at Monash)
- Dr Louis Jung (now at Google)
- Dr Nitzan Shany (now in a start-up in Tel Aviv)
- Dr Shaun Cloherty (now at the University of Melbourne)
- Dr Norbert Dommel (now at Cochlear)
- Dr Rylie Green (Imperial College)
- Chris Dodds (building a race car)
- A/Prof Socrates Dokos (UNSW)
- + Many thesis students



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The 2020 Summit – ‘One Big Idea’

One big idea

The group was tasked with further refining one of the top ideas put forward from the voting session on the Saturday. Following discussion, the group agreed on the following improved wording.

IDEA

5.112 Promote better commercialisation of intellectual property, by taking the lead in developing innovative health technologies, such as inventing a ‘bionic eye’ by 2020.

The group expanded on this to include promoting better translation of Australia's research efforts into commercial and health outcomes, underpinned by initial public investment and supported by increased private and philanthropic investment in R&D.

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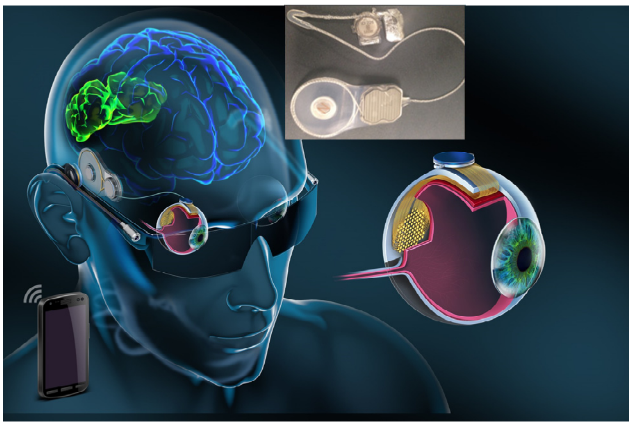

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Quality management

ISO13485 compliant Quality Management System (QMS) containing hundreds upon hundreds of commercial-ready documents providing:

- Raw material traceability
- Manufacturing work instructions
- Policies and procedures
- Specifications
- Risk assessments
- Change control
- Complete device design file
- Safety to the patient

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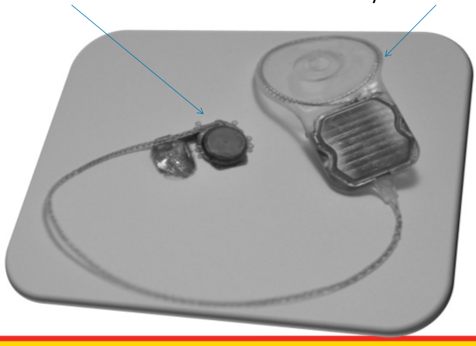
Phoenix^{99} (wide view) implant

98 channel visual stimulator

radio telemetry for data and power

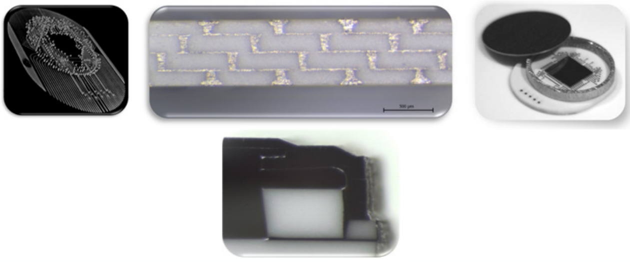


Longevity …

- In 1958, Arne Larsson (1915–2001) became the first to receive an implantable pacemaker
- He had a total of 26 devices during his life

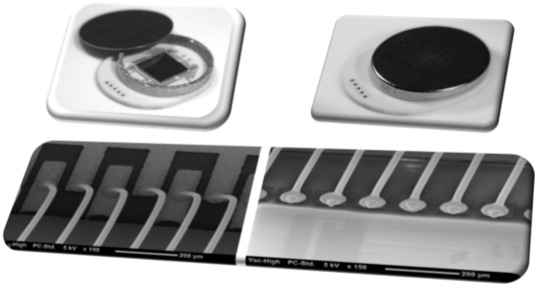
Device longevity

Encapsulation of electronics is done with novel feedthrough technologies that achieves the highest channel count of any known hermetic device in the world



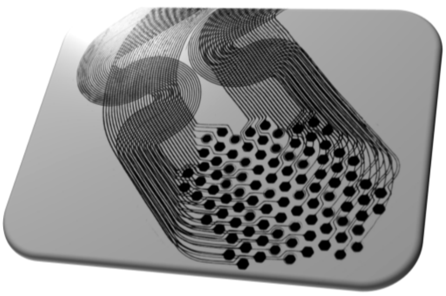
Protection of the patient and the implant

Devices are designed to have a 50 year functional lifetime



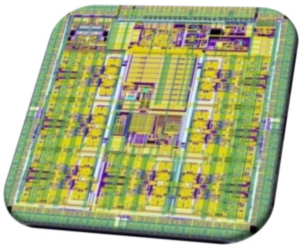
Electrode array

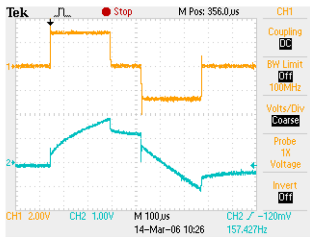
Underpinned by decades of research into micromachining and surgical processes. Precise, robust, and effective.



Implant electronics

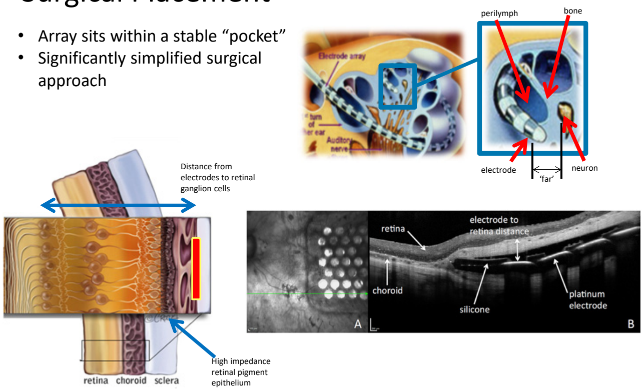
98 channels (sites) of neural stimulation. Charge balanced biphasic current waveforms used for safe stimulation.





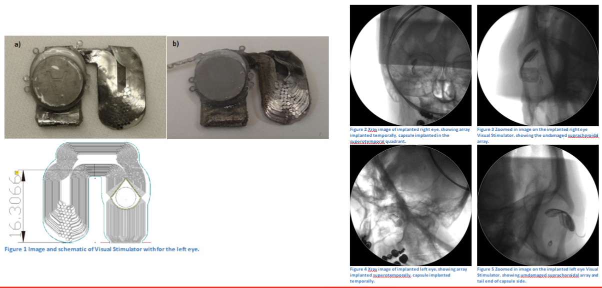
Surgical Placement

- Array sits within a stable “pocket”
- Significantly simplified surgical approach

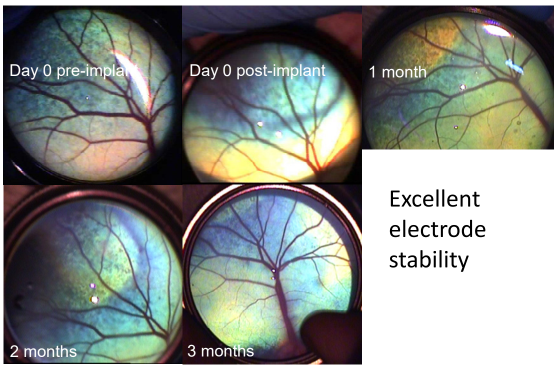


Human Cadaver Study - Surgical Development

Full procedure documented and refined in multiple studies in human cadaver subjects

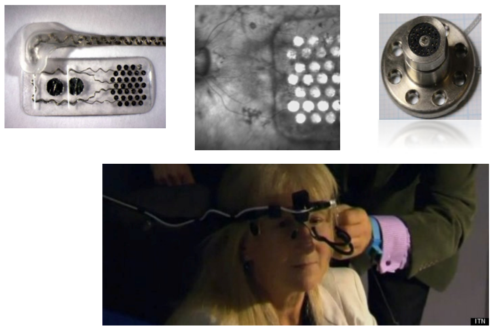


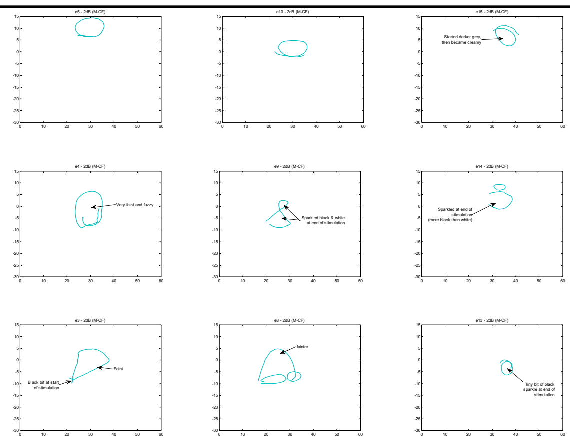
Indirect Ophthalmoscopy



Excellent electrode stability

Initial patient testing (n=3) with 22 electrode array using wide view surgical approach

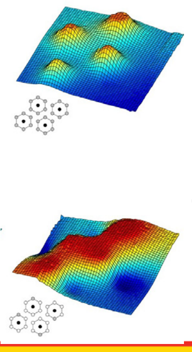


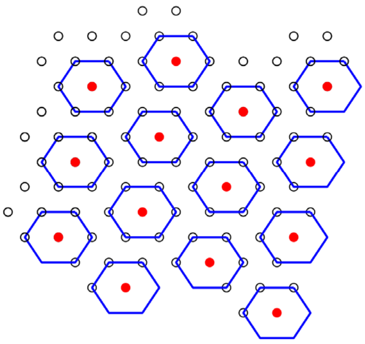


Stimulation strategy

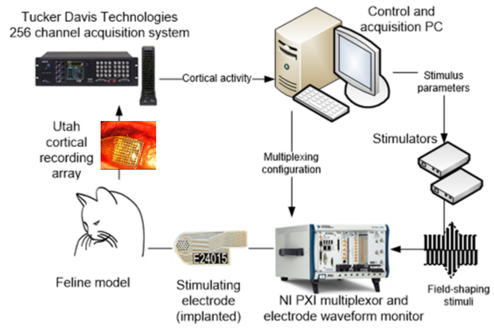
- Our goal is to provide the best visual experience, ensuring competitive advantage
- Some (out of many) technology differentiators
  - More phosphenes at once
  - Better control of phosphene shape

More Phosphenes at Once: Hexapolar Guards

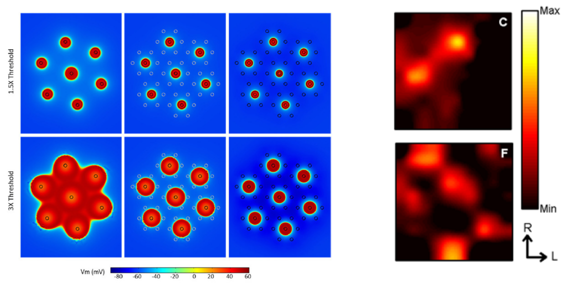




Stimulus Localisation



Control of Shape



System	Organisation	Stimulation channels	Exclusive use of materials already in long-term implants	One electrode leading to one unique percept	Intrinsic strategies for charge containment	Externally controlled processing (upgradable)	Potential to coexist with residual vision (e.g. AMD)	Simplified Surgery
	Phoenix[99] UNSW	98	✓	✓	✓	✓	✓	✓
	Epi-Ret 3	25	✗	✗	✗	✓	✗	✗
	Boston Retinal Implant Project	[illegible]	✗	✓	✗	✓	✓	✗
	Second Sight (ARGUS II)	[illegible]	✓	✗	✗	✓	✗	✗
	Retina-Implant AG	1.5k	✗	✗	✗	✗	✓	✗
	PIXIUM (was IMI)	[illegible]	✗	✗	✗	✓	✗	✗
	Nidek	[illegible]	✗	✗	✗	✗	✗	✗
	Osaka University	49	✓	✓ -	✗	✓	✓	✓

Electrode and device fabrication
Longevity
Current steering
Current steering
Current steering
Electrode placement
Electrode placement

Choose the statement that is **not** correct with regard a vision prosthesis:

a) An external vision processor reduces the need for revision surgery

b) Like the Cochlear device, the psychophysical interpretation by the cortex is crucial to device efficacy

c) One means of hermetically sealing the device electronics is to use silicone encapsulation

d) The spatial mapping of stimulation sites becomes more difficult as one moves the site of stimulation more centrally from the retina to the cortex

In order to test the efficacy of the implant in evoking a visual response in an animal model:

a) A sheep is trained to bleet every time a visual stimulus is perceived

b) Electrocardiogram recordings are made

c) Measurement of the electrical activity of the visual cortex can be used

d) It is necessary to estimate the impedance of the electrode-tissue interface

Encapsulation of the proposed implantable vision processor electronics would consist of:

a) Cofiring with manganese oxide and titanium dioxide to increase the sintering temperature
b) A titanium shell
c) A hydroseal bag
d) An alumina-based ceramic

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A possible site for a visual prosthesis would **not** include:

a) Sub-retinal space
b) Auditory brain stem
c) Visual cortex
d) Lateral geniculate nucleus

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The key processing element of the implantable device is:

a) An image processor
b) A Babbage engine
c) A CMOS VLSI
d) An application specific integrated circuit (ASIC)

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Which is **not** true for a balanced, biphasic, constant-current stimulus?

a) Stimulus voltage increases with increasing electrode-tissue impedance
b) Provides for maximal charge recovery
c) Prolongs implant (electrode) longevity
d) Increases the likelihood of an offset voltage appearing across the stimulating electrodes after the stimulus has finished

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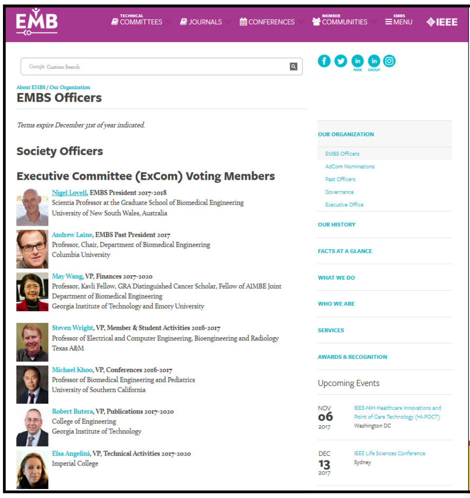

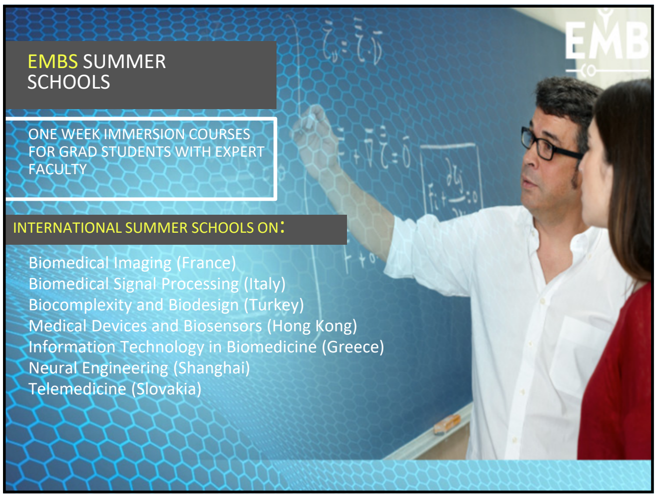

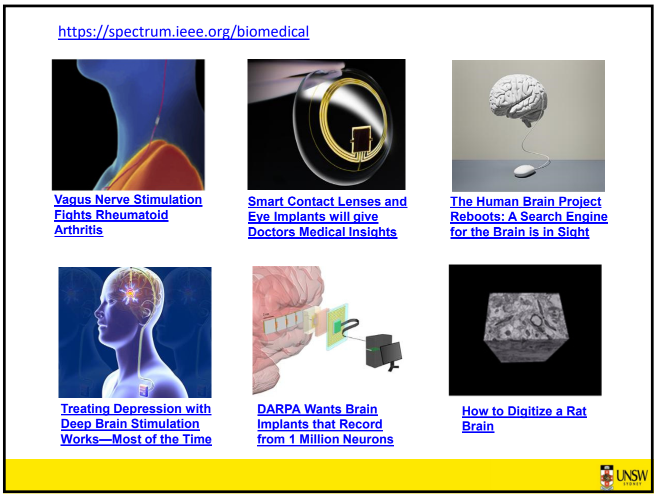

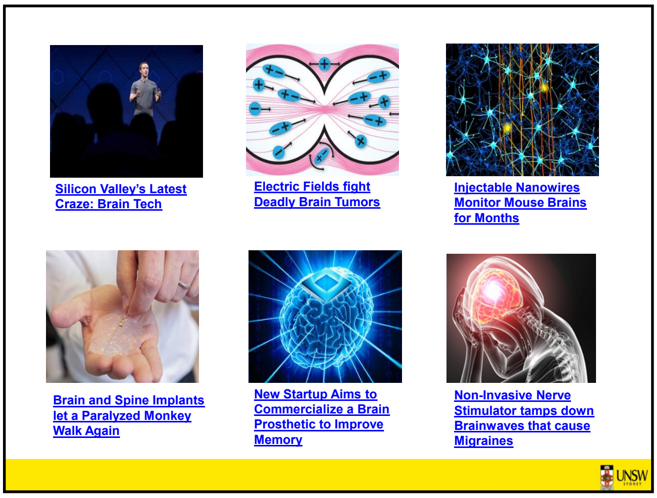

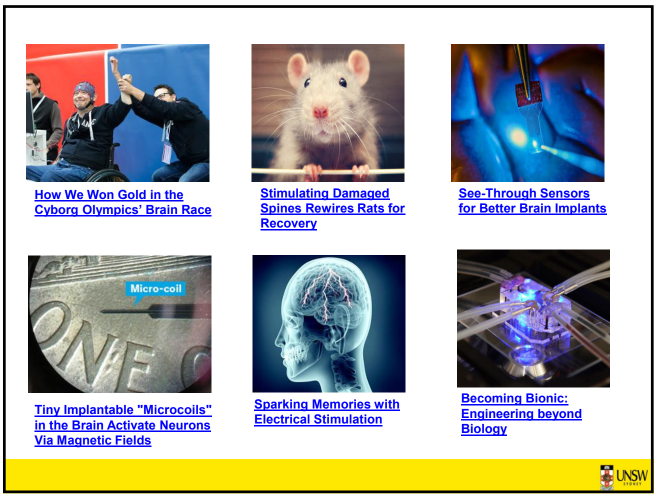

Summary

- Tutorials will help you understand biopotential (ECG) recordings and the fundamentals and underlying mathematics of action potential generation
- Revise basic neurophysiology, physiology of the visual system and the bionic eye (as one representative example of an implantable neuroprosthesis)

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