System-Integration: Examples of Innovative Health Products

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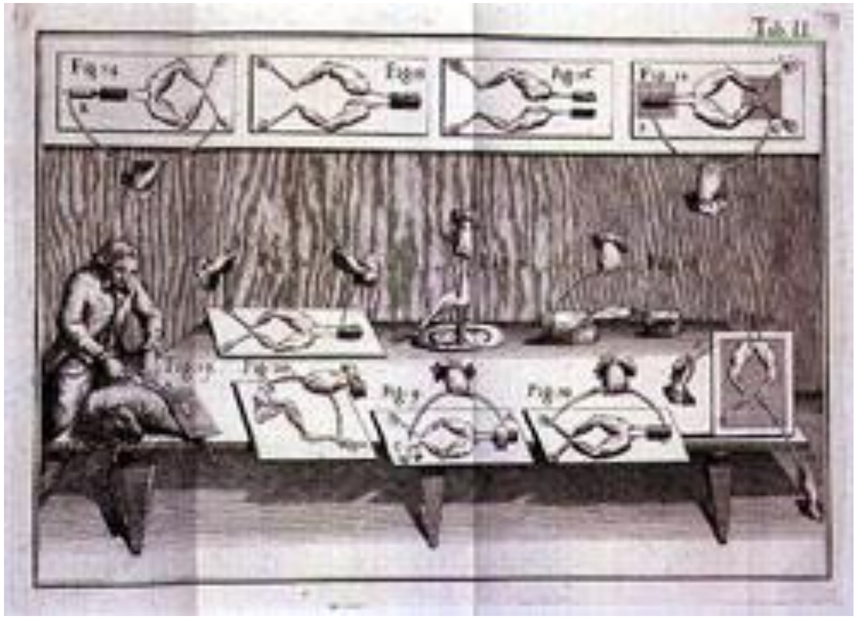
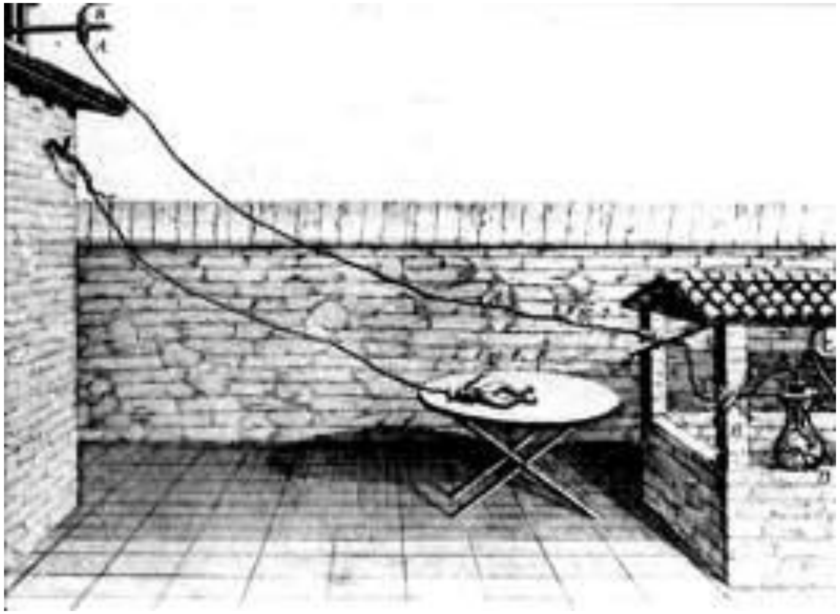
Outline

- Electrical stimulation of nerves
- BMES ERC
- Retinal Prosthesis
- Spin-offs
  - Improved electrode materials
  - Implantable mini-pump
- Lessons learned

Volta and Galvani, 1800's

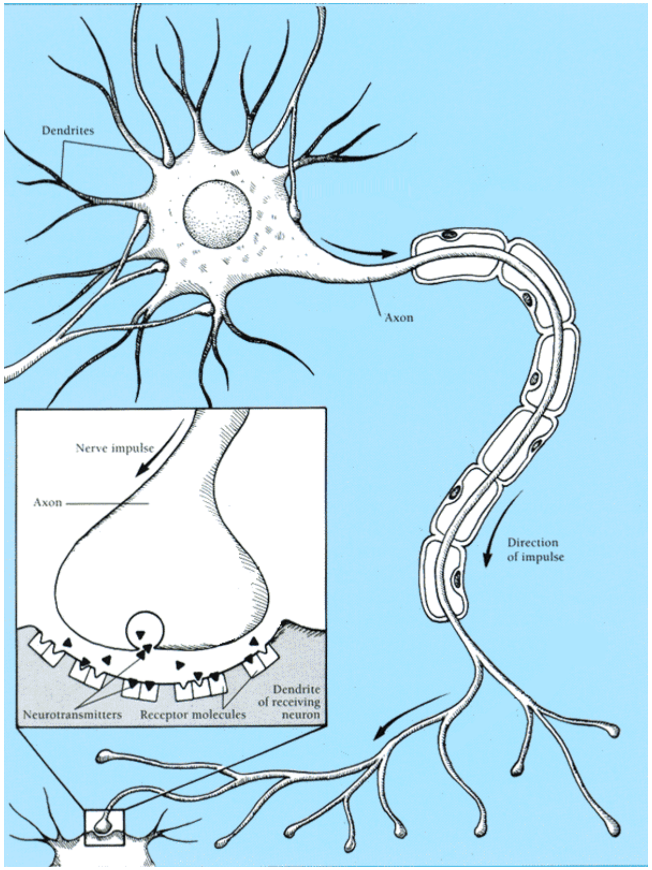
- Stimulation of muscle in frogs
- Volta stimulated his ears with electrodes, noted a "bubbling" sound



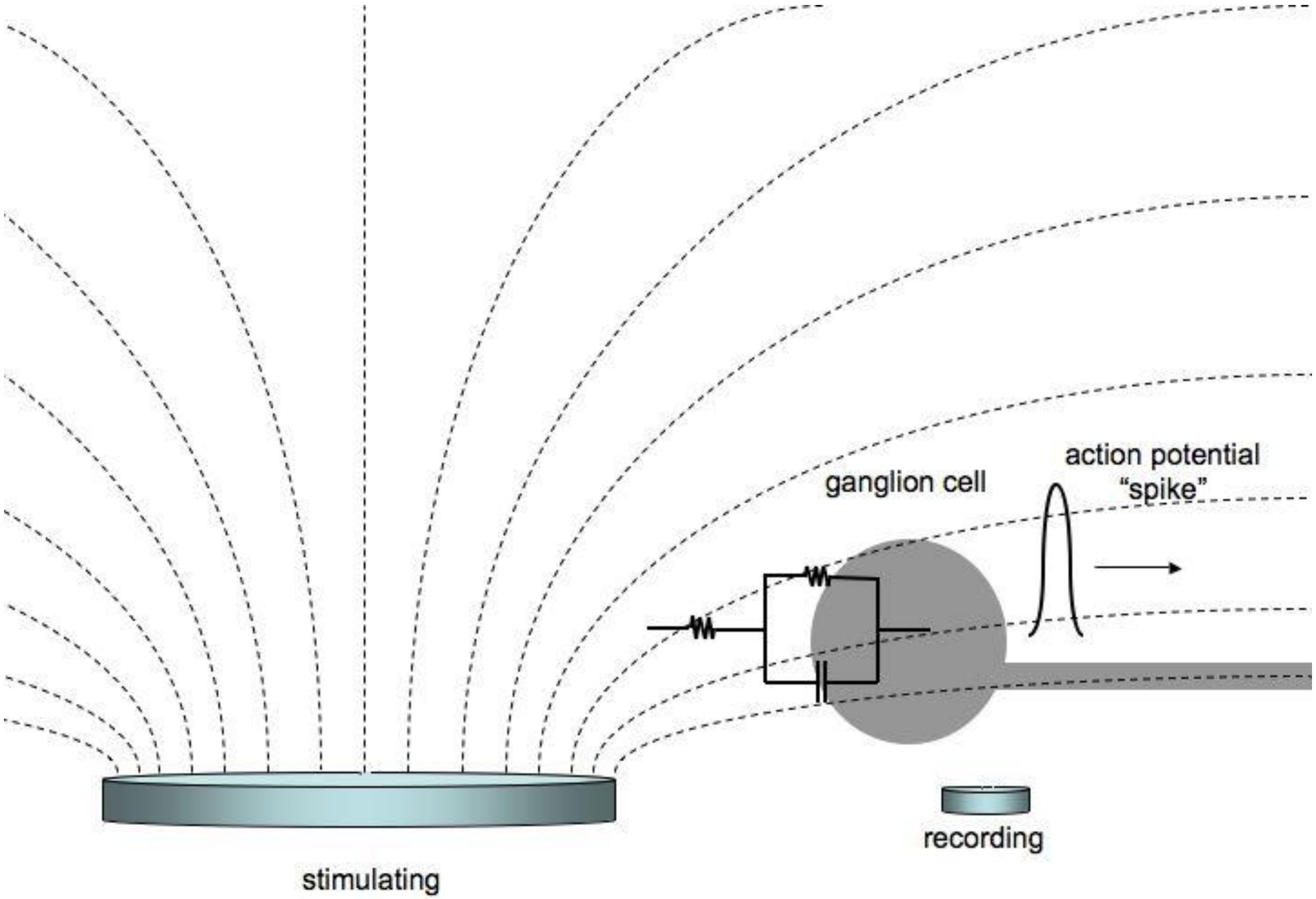


Nerve Anatomy and Physiology

- Common features
  - Dendrites, soma, axon
- Synaptic connection to other nerves
- Cell membrane
  - Electrical potential
  - Variable membrane conductance used for signal propagation
- Slow signaling (ms time scale)



Electric fields applied by microelectrode can activate nerve cells

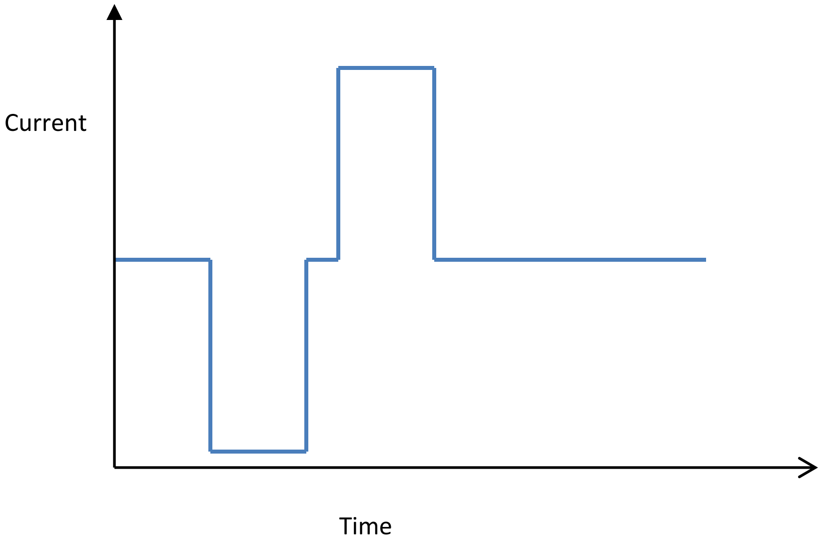


Constant Current Stimulation

- Neural stimulation is accomplished by a constant current pulse, typically.
- Charge is the product of current and time.
- Results in constant electric field

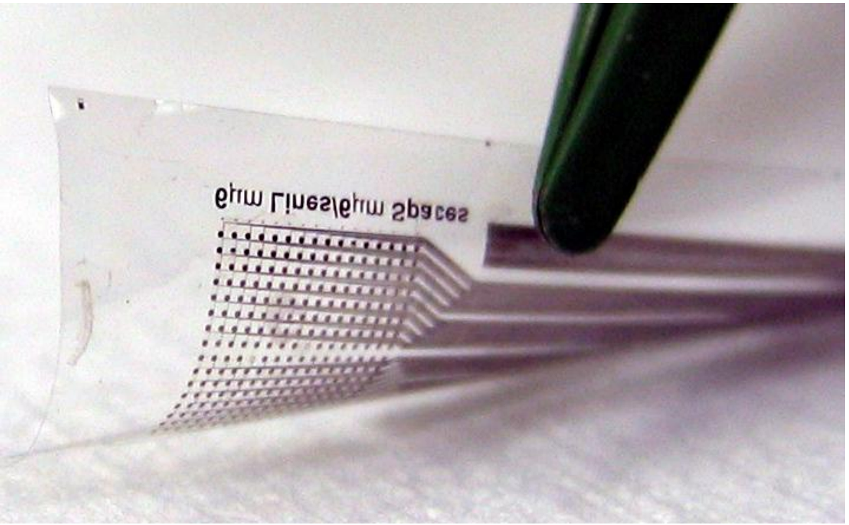
  $$E=\rho*J$$

- Charge balance: product of stimulus amplitude and stimulus pulse duration should be the same for the negative and positive pulse to ensure that no net charge accumulates on the interface (Lilly, 1961)



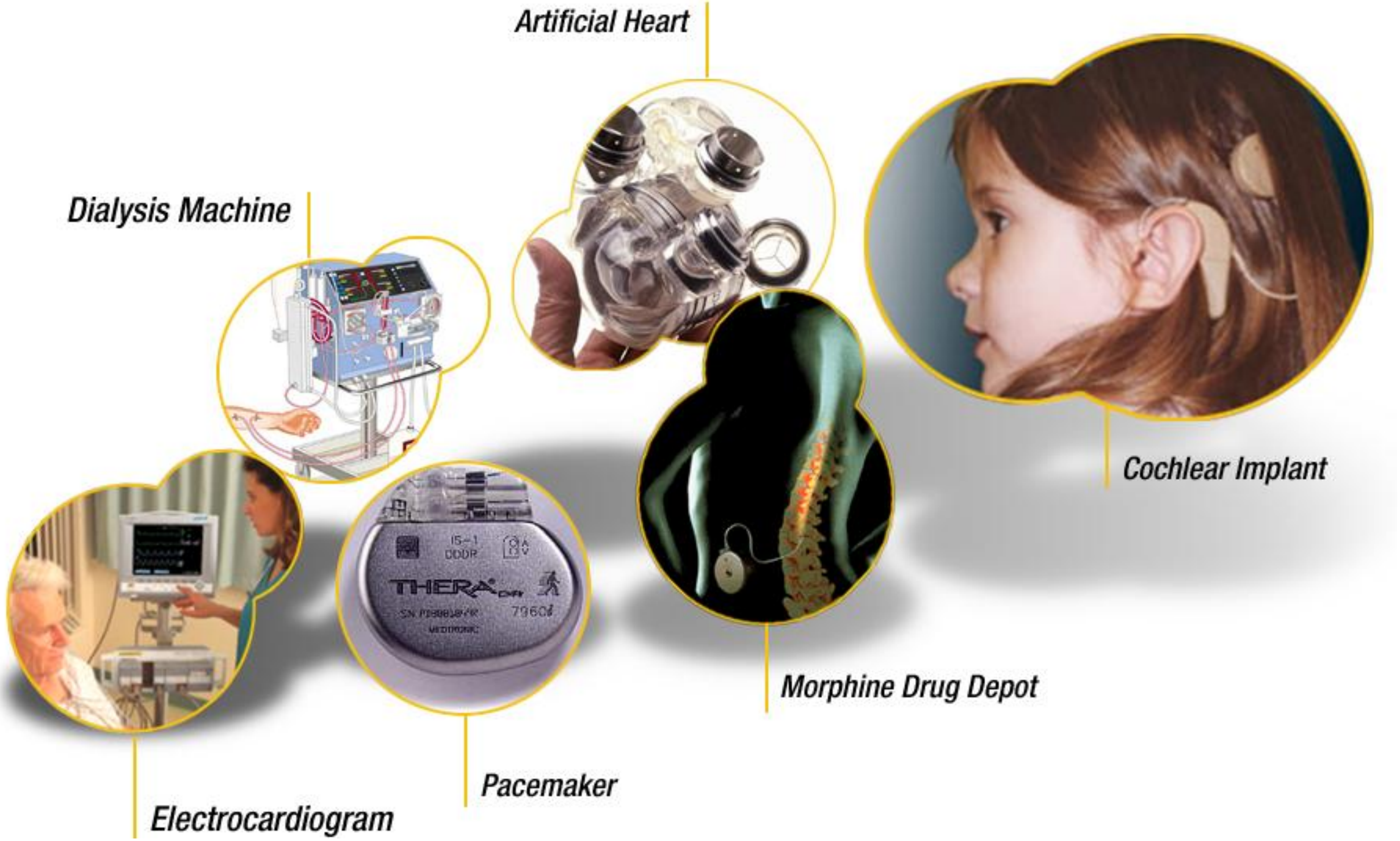
Common Microelectrode Materials

- Platinum commonly used, cochlear implants, DBS, spinal cord
- Iridium oxide used in pacemakers, BIONs
- Requirements
  - Non-corroding
  - Safe charge transfer
  - Can be integrated into system



Pt on Parylene
256 Electrode Array
YC Tai - Caltech

Advances in Medical Electronics



Pacemakers, the first electrical implantable

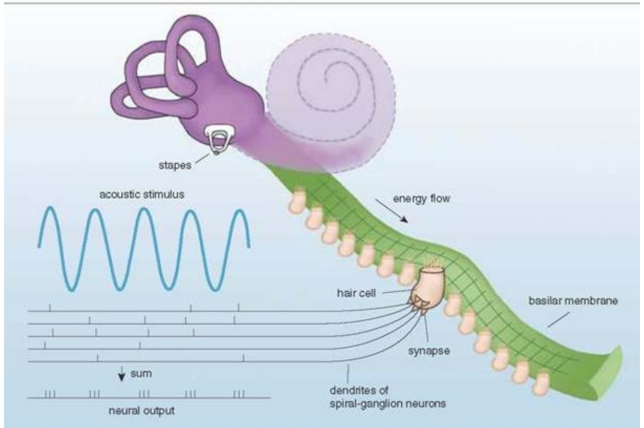
- First versions not totally implanted in the body, needed AC power
- 1957 – battery powered, transistorized
- 1960s – totally implantable pacemaker, battery power

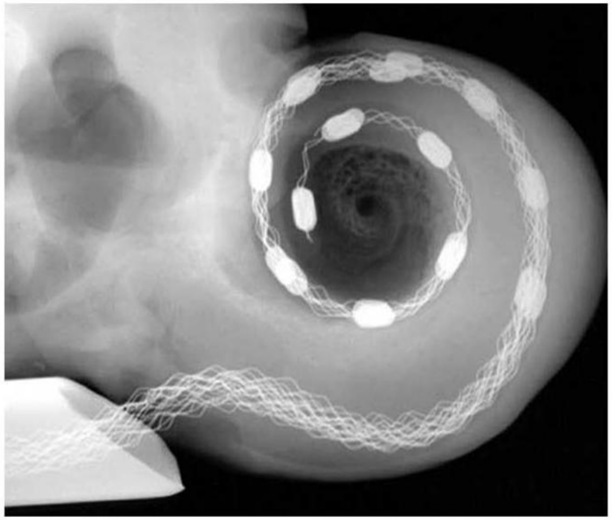
Dr. C. W. Lillehei with young patient

Cochlear Implants

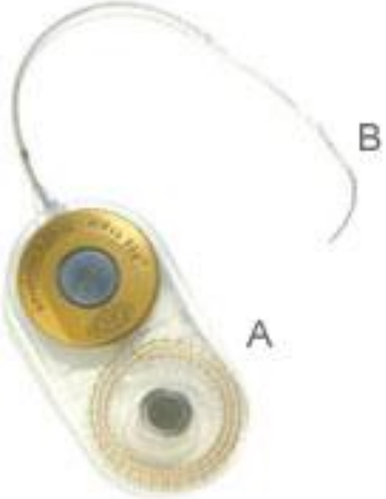
Initial report of stimulation of the cochlea by Djourno and Eyries, late 1950s

- Patients could distinguish between different sounds
- Today's implants stimulate the cochlea at up to 32 locations, but usually use fewer



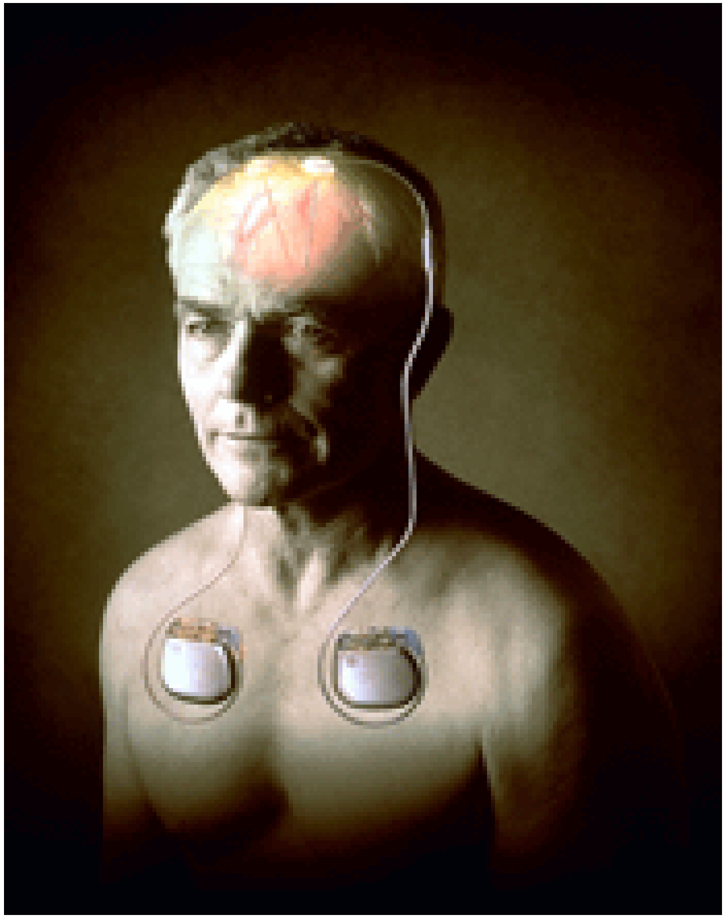


Examples of Cochlear Implants



Deep Brain Stimulation

- Thalamic stimulation to treat movement disorders (dystonia, chorea, tremor), approved single side 1997, double sided 2002
- Remarkable results, simple device
- Interesting side effects in some cases, signs of depression



Limitations of Current Medical Implants

- Large hermetic cases with a relatively small number of feedthroughs
- Long lead wires
  - Infection path
  - Prolongs surgery
- Large hand-made electrodes (limited scalability)

© Medtronic, Inc. 2009

Mission of BMES ERC

The human nervous system when damaged does not heal well if it heals at all

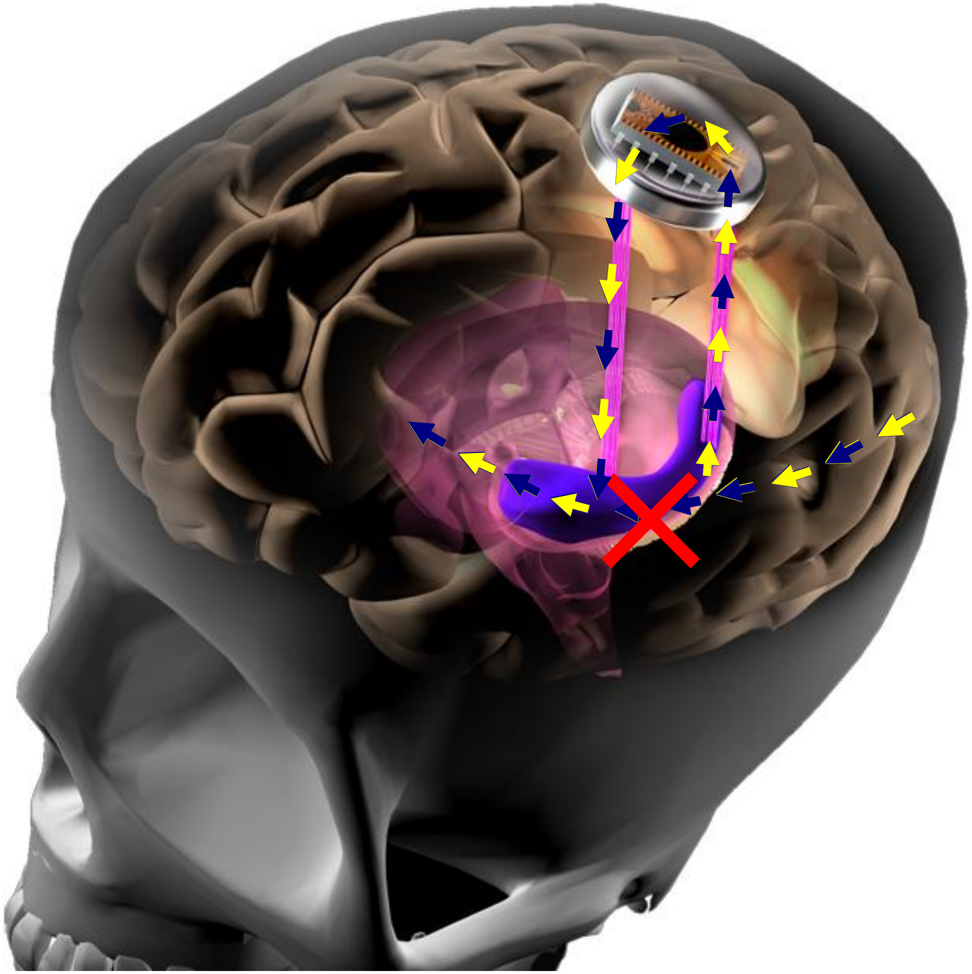
Biomimetic microelectronic systems will form direct high-density interfaces with the human nervous system to restore lost function

Cortical Prosthesis Project (PI – Ted Berger)

Cortical Prosthesis Goal: Develop biomimetic models of hippocampus to serve as neural prostheses for lost cognitive/memory function

General Strategy:

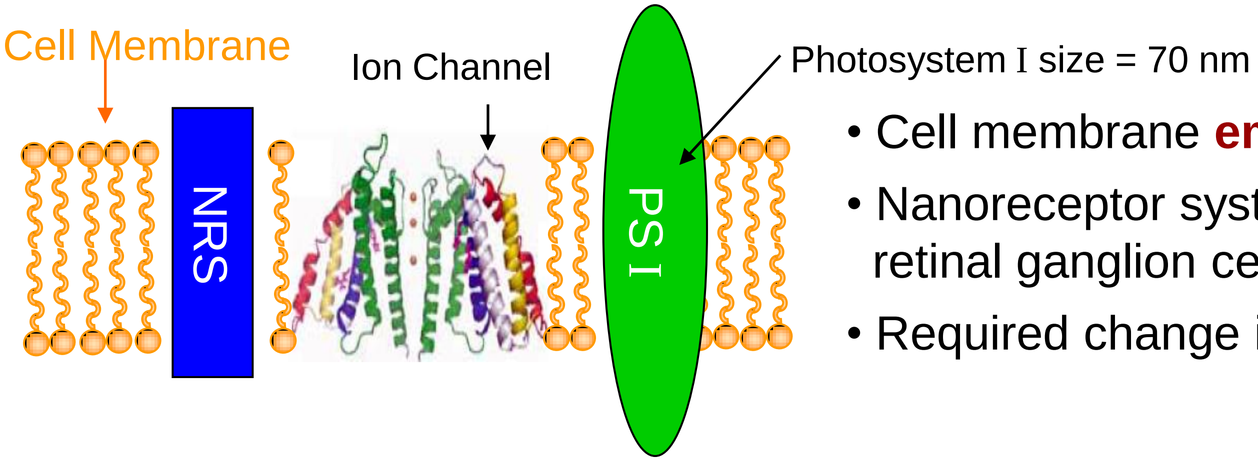
1. **Biomimetic model/device that mimics signal processing function of hippocampal neurons/circuits**
2. **Implement model in VLSI for parallelism, rapid computational speed, and miniaturization**
3. **Conformal multi-site electrode recording/stimulation arrays to interface biomimetic device with brain**
4. **Goal: to “by-pass” damaged brain region with biomimetic cognitive function**



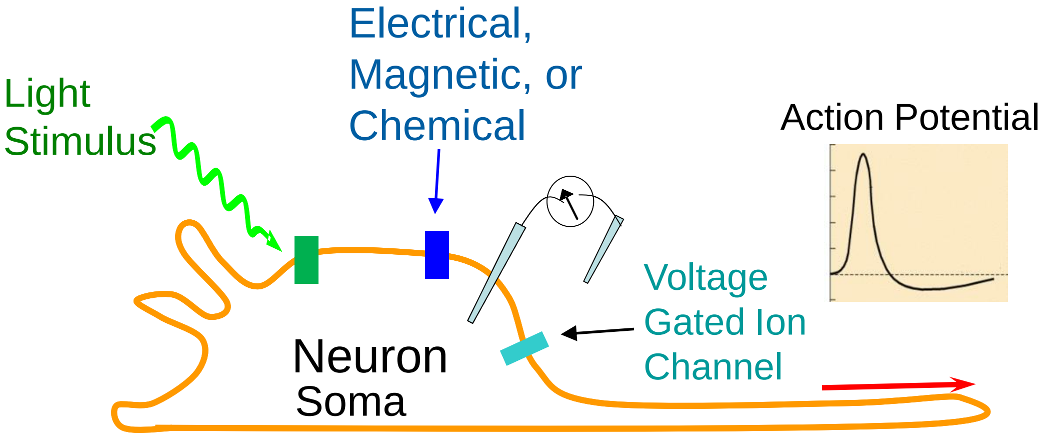
Cellular Prosthesis: (PIs – Robert Chow, Mark Humayun) An approach to interface directly with individual neurons

Nano Artificial Receptor System (10's of nm):

A nanoscale engineered *system* that depolarizes neurons in response to ambient light or other stimulation.

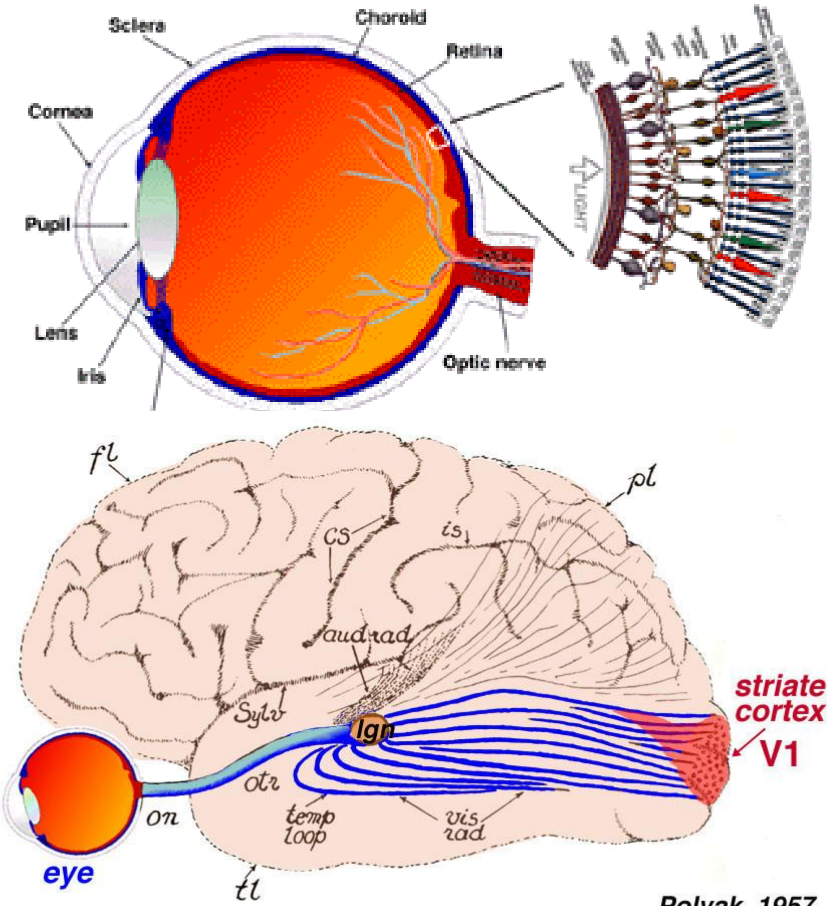


- Cell membrane **embedded or attached**
- Nanoreceptor system (NRS) depolarizes retinal ganglion cell in response to light
- Required change in voltage ~15 mV



- Upon stimulation NS causes **membrane potential change** to trigger opening/closing of voltage-gated ion channels. This in turn causes the neuron to fire an action potential propagating down the axon.

Human Visual System and Retinal Blindness



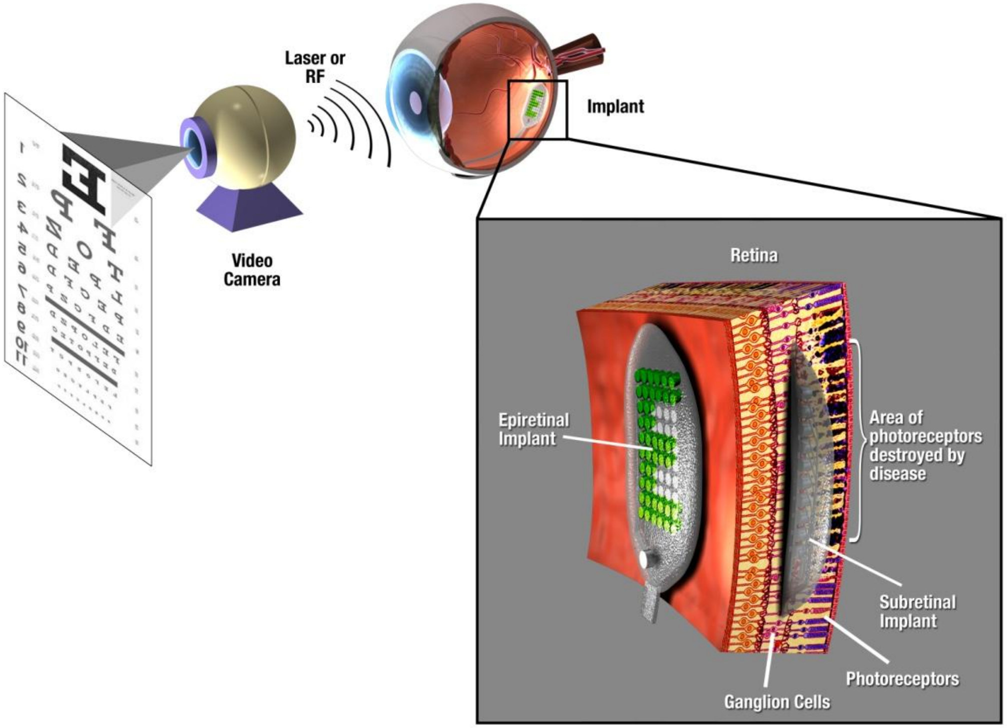
Polyak, 1957

Webvision, Kolb, Fernandez, and Nelson, 2003.

- Retina is a light sensitive neural network
- Diseases such as Retinitis Pigmentosa (RP) and Age-related Macular Degeneration (AMD) primarily affect the photoreceptors, are both presently incurable, and render 100,000s blind each year

Retinal Prosthesis
Systems Level Description

- External camera/image processor detects image and performs conversion to digital information
- Telemetry link between external and implanted units
- Implanted unit recovers power and data
- Implanted unit applies commanded stimulus pattern to the retina via a microelectrode array on the surface of the retina



Retinal disease

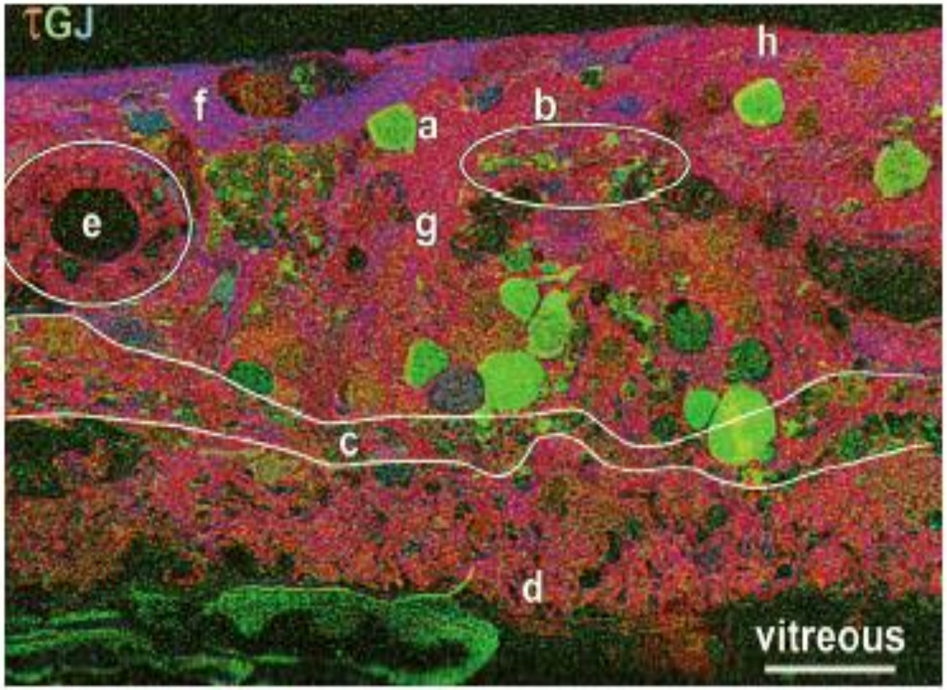
- Age-related macular degeneration (AMD) and retinitis pigmentosa (RP) are significant medical problems, blinding millions around the world
  - RP is a family of diseases with over 100 gene mutations resulting in photoreceptor loss
    - Begins with night blindness and peripheral vision loss, followed by central vision loss
  - AMD also has a genetic component, results in loss of photoreceptors in the central visual field, is more common than RP, but less severe

Mean Cell Count from Post-Mortem RP Eyes

Group	**Age,y**	**Outer Nuclear Layer**	**Inner Nuclear Layer**	**Ganglion Cell Layer**
Moderate	73.56±11.19	12.91±17.59*	37.61±10.45	9.21±4.2*
Severe	76.17±8.89	2.33±2.95*	33.37±9.71*	5.72±4.13*
Normal	75.58±10.12	46.9±12.73	42.56±11.56	19.16±5.91
P (Using F test of Variance)	0.83	<0.01	0.08	<0.001

Humayun and colleagues, 3 papers 1992-1999

Remodeling in Retinal Degenerations



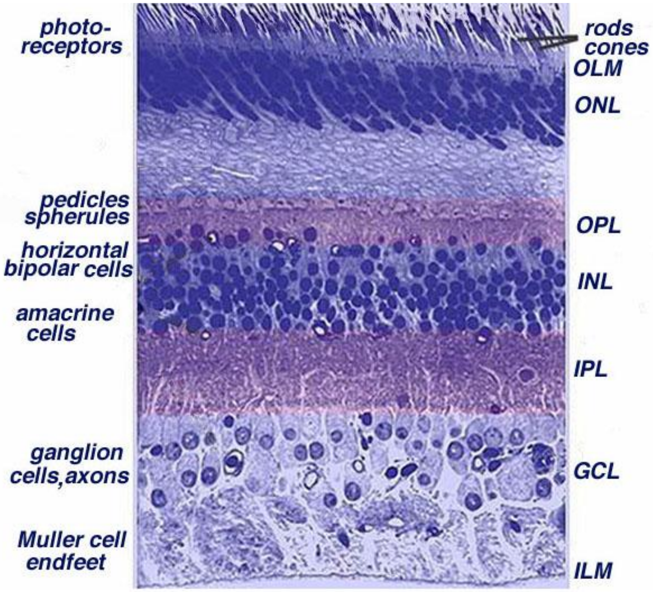
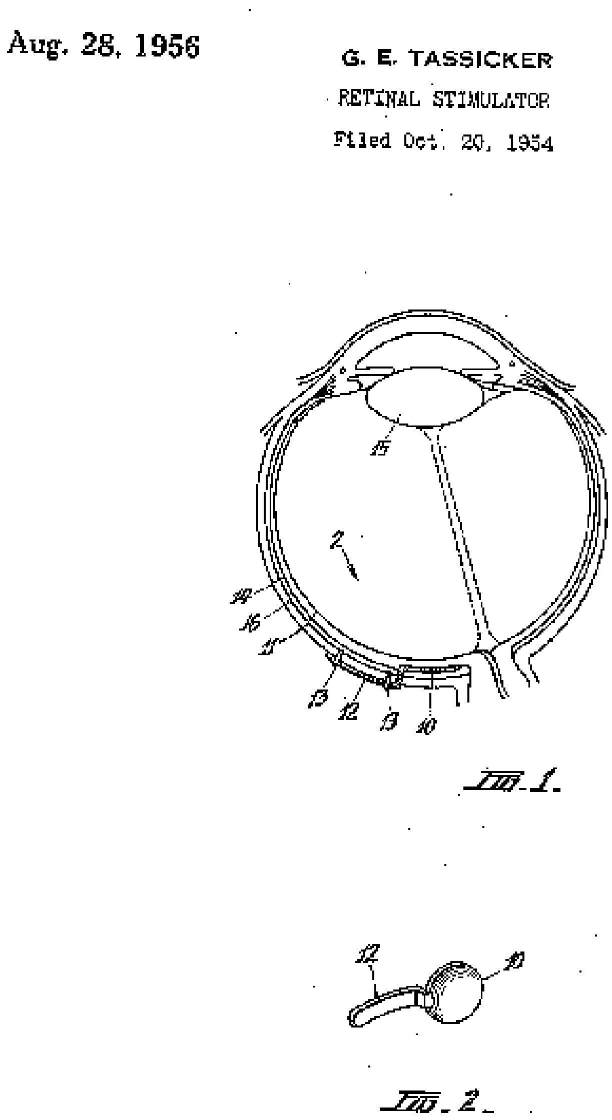


Fig. 3. Light micrograph of a vertical section through central human retina.

Early Implants

- Tassiker Patent, 1956
- Brindley’s implantation of blind subject with 80 electrode cortical stimulator, 1968
- NIH NPP stimulation with penetrating electrodes, 1990s (Bak, 1990, Med. Biol. Comp., Schmidt 1996, Brain)



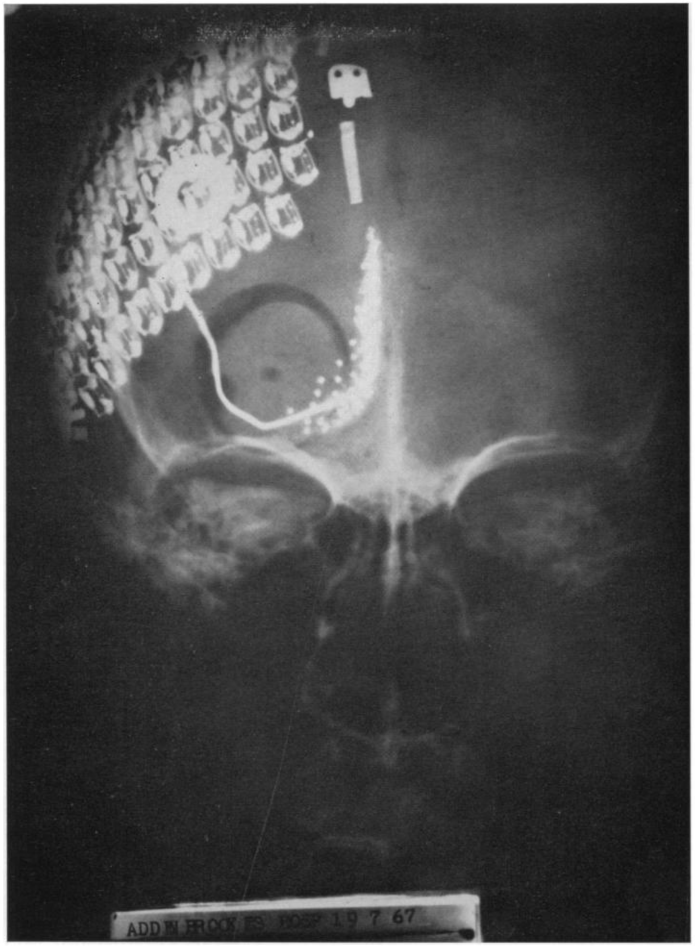
Aug. 28, 1956

G. E. TASSICKER

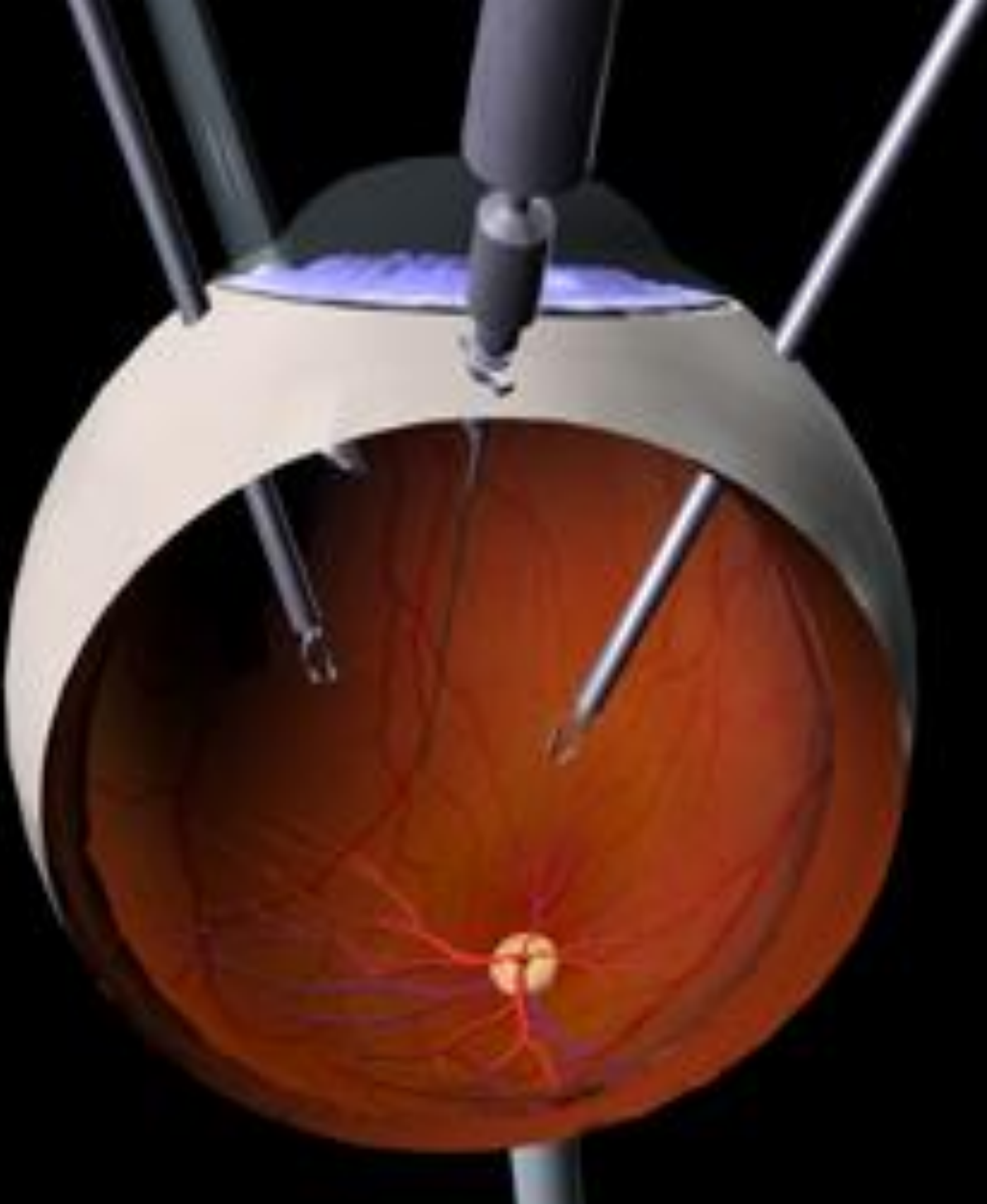
RETINAL STIMULATOR

Filed Oct. 20, 1954

Brindley Subject X-Ray



Brindley and Lewin,
J. Phys. 1968



Summary Data from Acute Trials

Subject	**Condition**	**Vision**	**Percept**	**Color**	**Charge (μC)**
HC	RP	NLP	Letter	Yellow-Green	0.4
AD	Ret-Degen	LP	?	?	0.95
CC	RP	NLP	Matchhead	Yellow	0.16
RS	RP	LP	Pin	Yellow	3.2
WG	AMD	NLP	Pencil	White	6.0
PS	RP	LP	Pea	Yellow	2.8
BC	RP	LP	Pin	Yellow	1.6
RJ	RP	LP	Pin	Yellow	1.8
BH	RP	NLP	Pin	White	1.1
AB	AMD	20/400	Pin	White	0.3
CS	RP	LP	Pin	Blue	2.4
VO	RP	LP	Pin	Yellow	1.0
HW	RP	LP	Pin	White	1.2
JT	RP	LP	Box	White	1.4
JL	RP	LP	Firefly	White	0.2

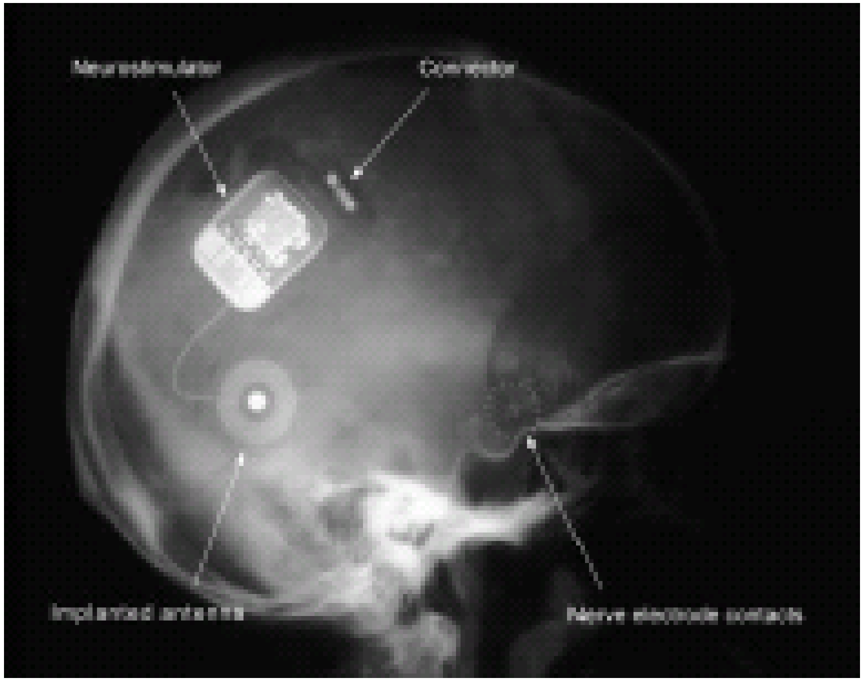
Visual Cortex Implant

- Troyk research group at IIT has implanted several NHPs and demonstrated some efficacy (Bradley, et al, J Neurophysiol. 2005)
- Normann research group at Utah, UEA based approach (Warren and Normann, Vision Res. 2005)

http://neural.iit.edu/intro.html

Optic Nerve Prosthesis

- Veraart research group in Belgium has been testing in 1 subject since 1999
- 4 contact, nerve cuff
- Subject can locate objects with camera by scanning visual field
- Second subject with cuff on outside of optic nerve sheath failed to generate useful perceptions



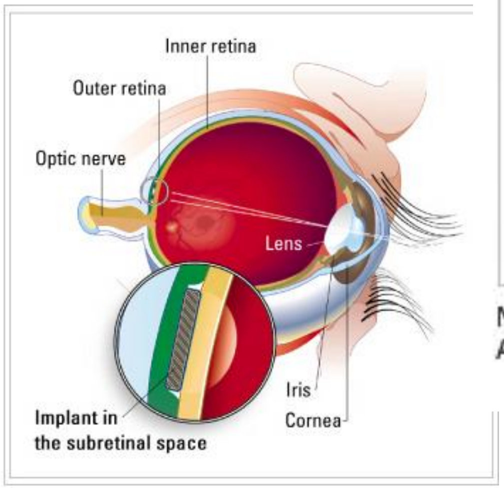
Veraart, et al. Artif. Organs, 2003

Chronic Retina Implant Studies

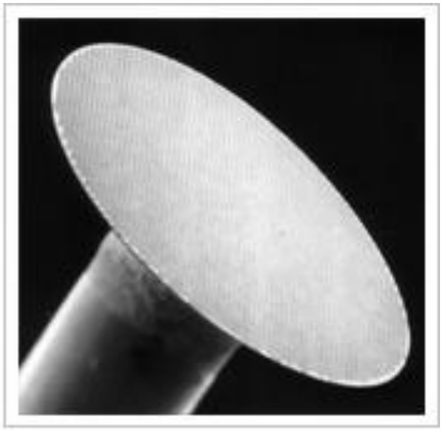
- Optobionics, Inc. (defunct)
- Doheny-USC, Second Sight Medical Products, Inc.
- Intelligent Medical Implants (Swiss)
- Retina Implant, GmbH (German)
- Companies run clinical trials, due to cost, engineering rigor required for implantable medical device, regulatory issues
  - Exception, AMI BION clinical trials

Optobionics

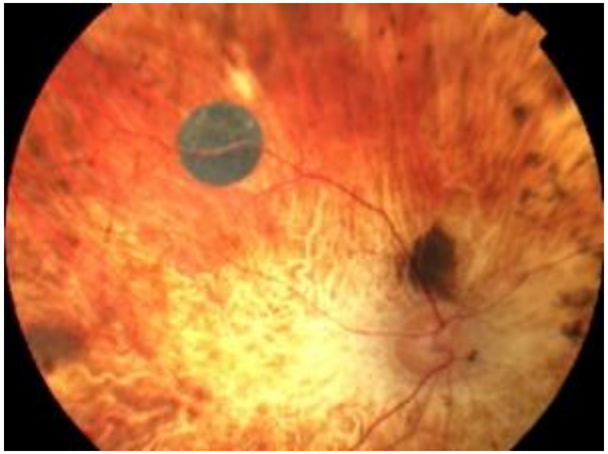
- Subretinal microphotodiode array in 30 subjects
  - Subjective improvements
  - Some subjects persistent improvement, others transient
  - Implantation appears safe
  - Neurotrophic effect suggested, but not shown conclusively in animals
- Theoretically not practical for neural stimulation, If retinal irradiance is 0.9 mW/mm^2 (direct sunlight, Palanker et al 2005), then stimulus current from a 20 um microphotodiode is 40 pA (80% efficiency of microphotodiode)



Drawing by Mike Zang

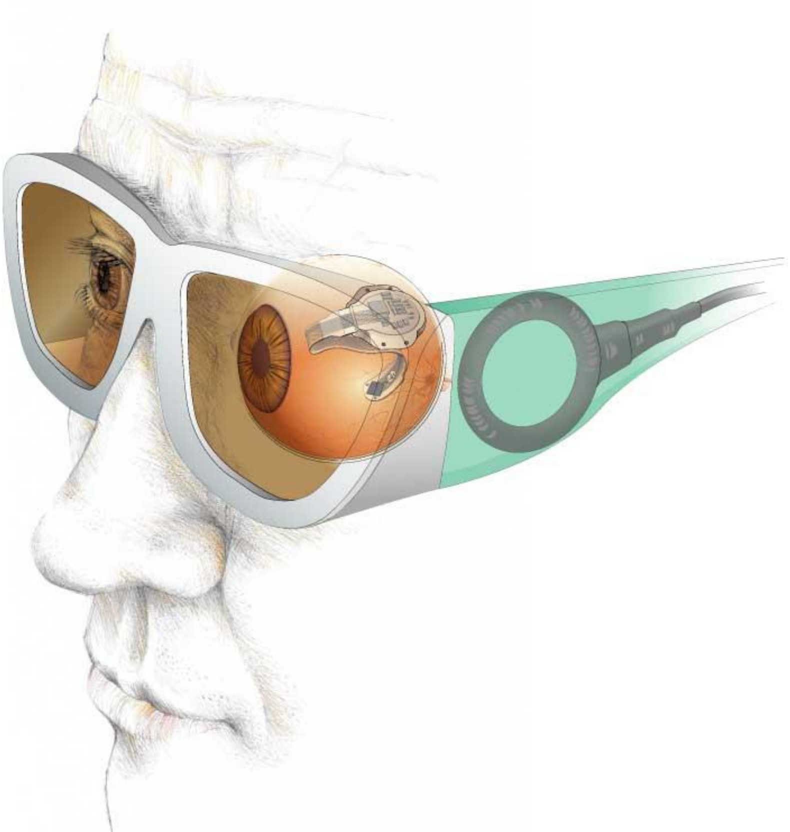


Magnified image of an ASR® device



Intelligent Medical Implants

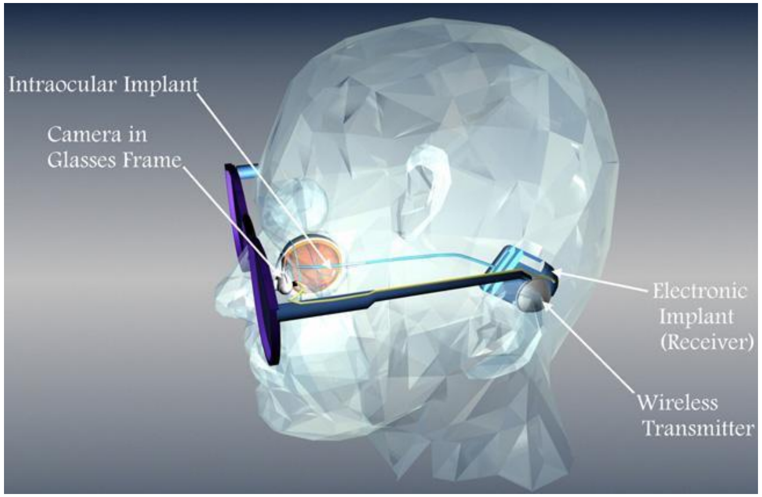
- Epiretinal
- Reported 7 test subjects implanted with 49-channel device
- 10s on nC needed for perceptual threshold
- No camera system
- Infrared data link
- Questionable packaging lifetime, technology (18 month proven)
- Next step, integrate camera



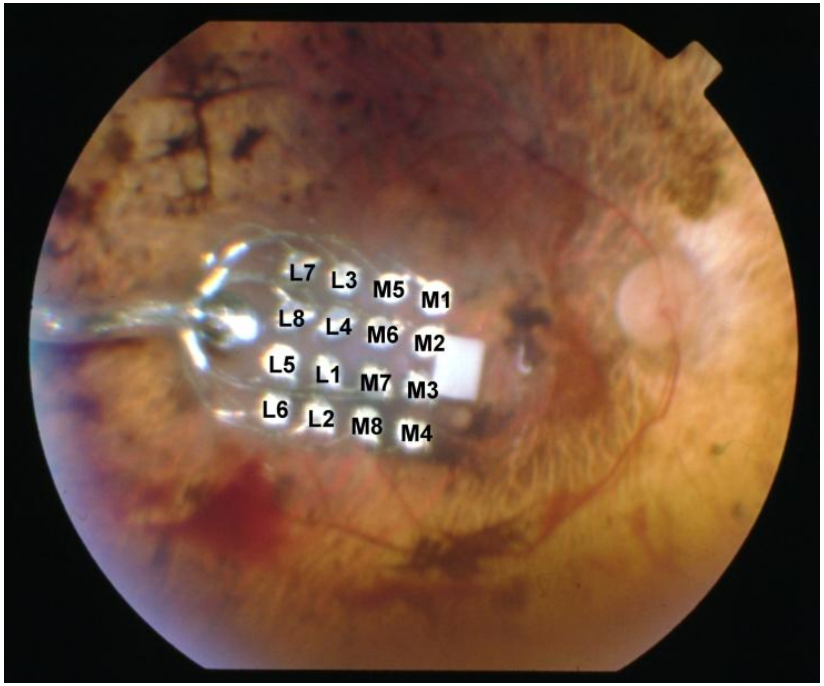
http://www.intmedimplants.com/

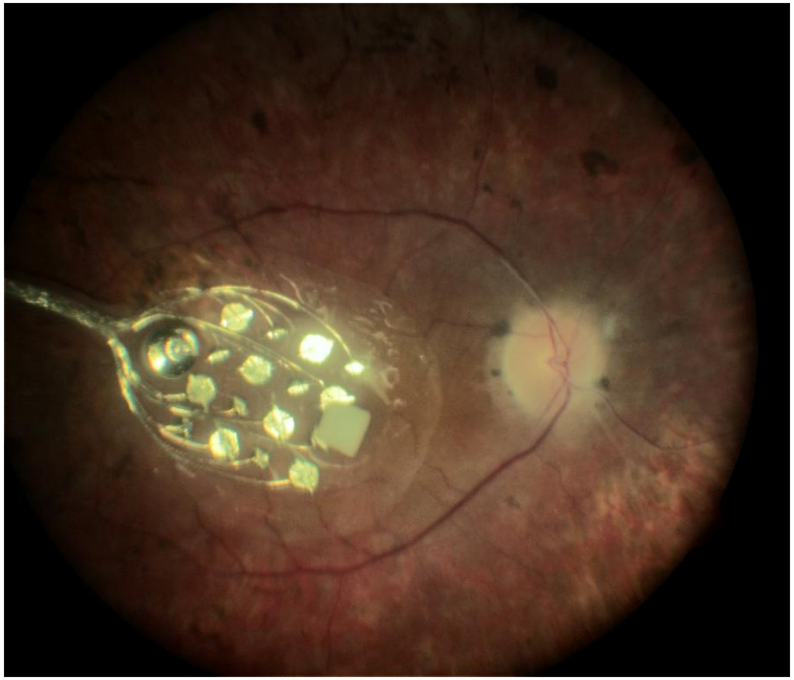
ARGUS I Prototype

- Modified cochlear implant
- Implanted in 6 subjects at USC 2002-2004 as part of FDA approved feasibility study
- Light detection shown in all electrodes

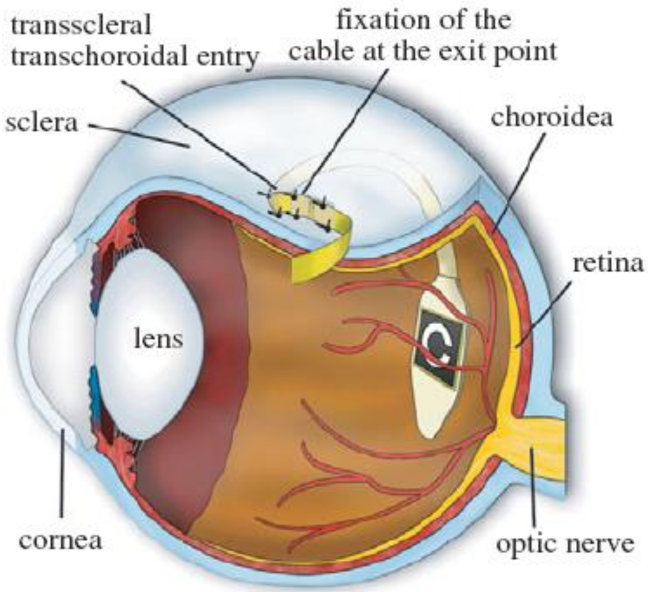


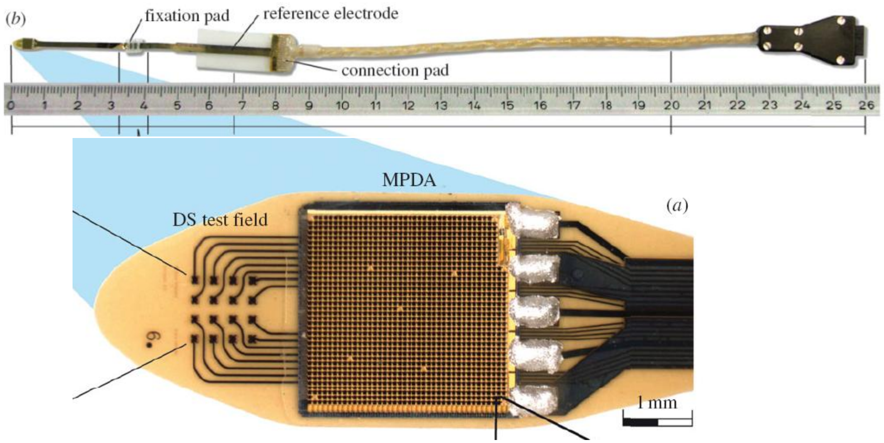
ARGUS I Electrode Array

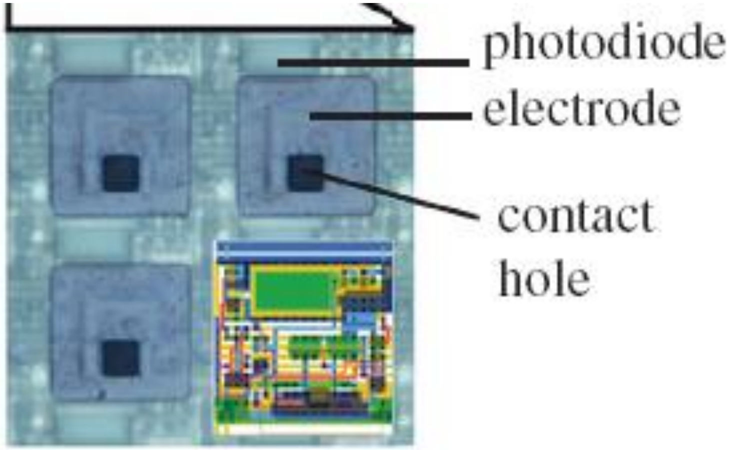


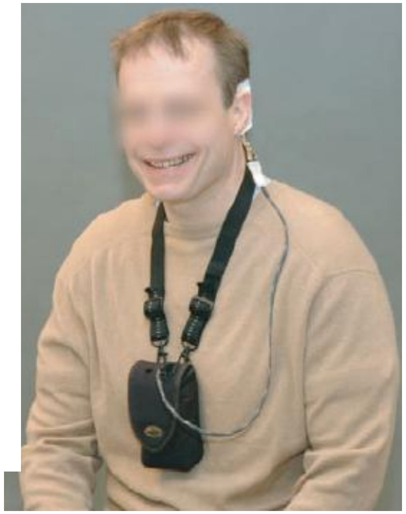


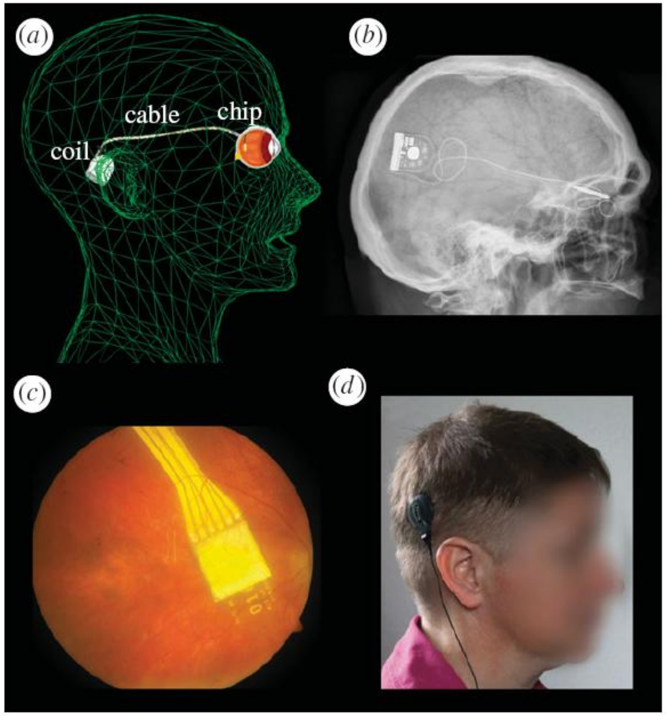
Subretinal Prosthesis Clinical Trials

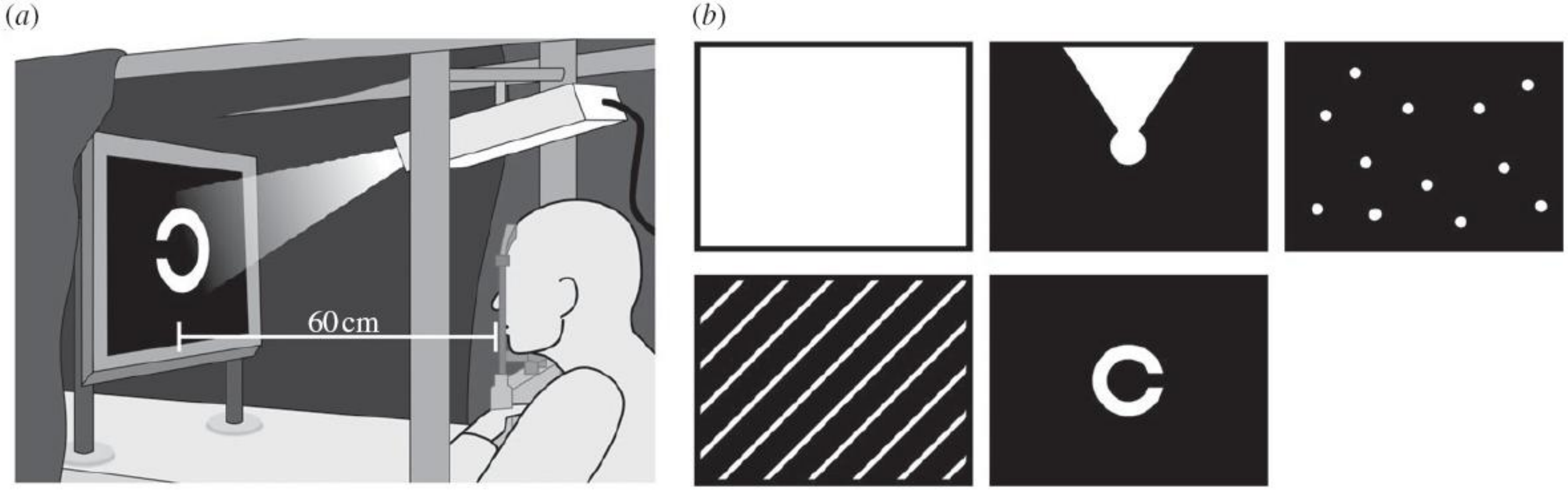












(*c*)

	S2	S3	S4	S5	S6	S7	S8	S9
light	yes	yes	yes	yes	yes	yes	yes	yes
location	yes	no	yes	yes	yes	yes	yes	yes
motion	no	no	3° per sec	no	7° per sec	5° per sec	35° per sec	5° per sec
grating acuity	no	no	0.33 cpd	0.1 cpd	0.3 cpd	0.5 cpd	3.3 cpd	1.0 cpd
Landolt C	no	no	no	0.01	no	no	0.04	no

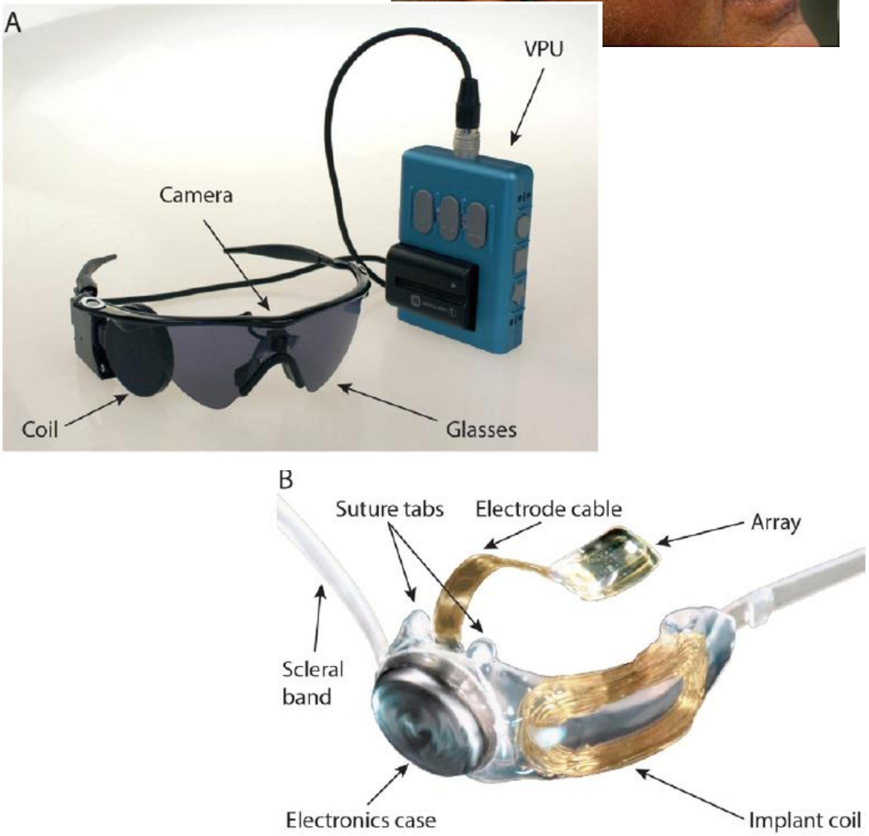
Argus II Clinical Trial

- 32 Subjects at 10 centers in North America and Europe (proceeded by 6 subject Argus I trial at USC)
- All subjects see phosphenes with the System
- All subjects have used the System at home
- Studies to be reviewed (Humayun et al. 2012)
  - Object Localization
  - Motion Discrimination
  - Orientation and Mobility

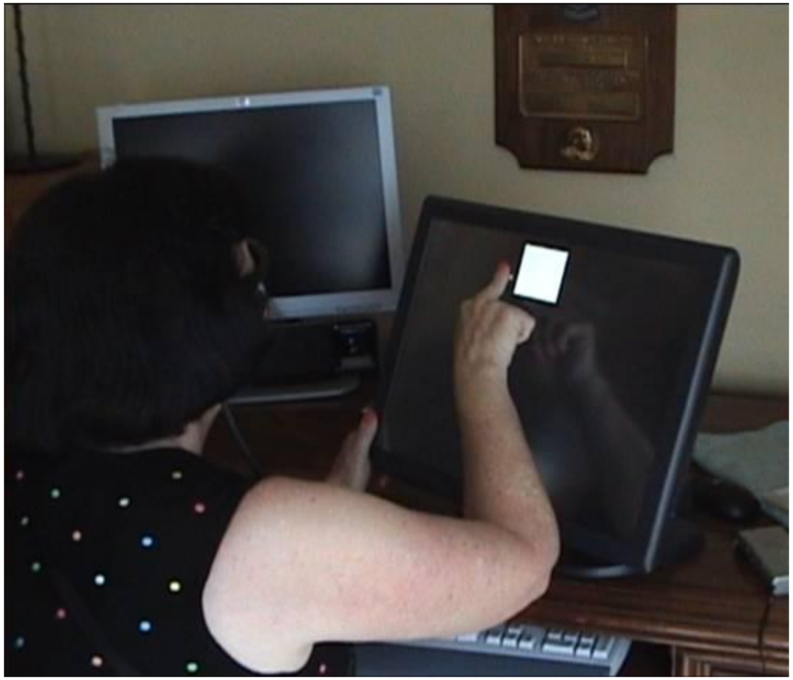
Argus II Retinal Prosthesis

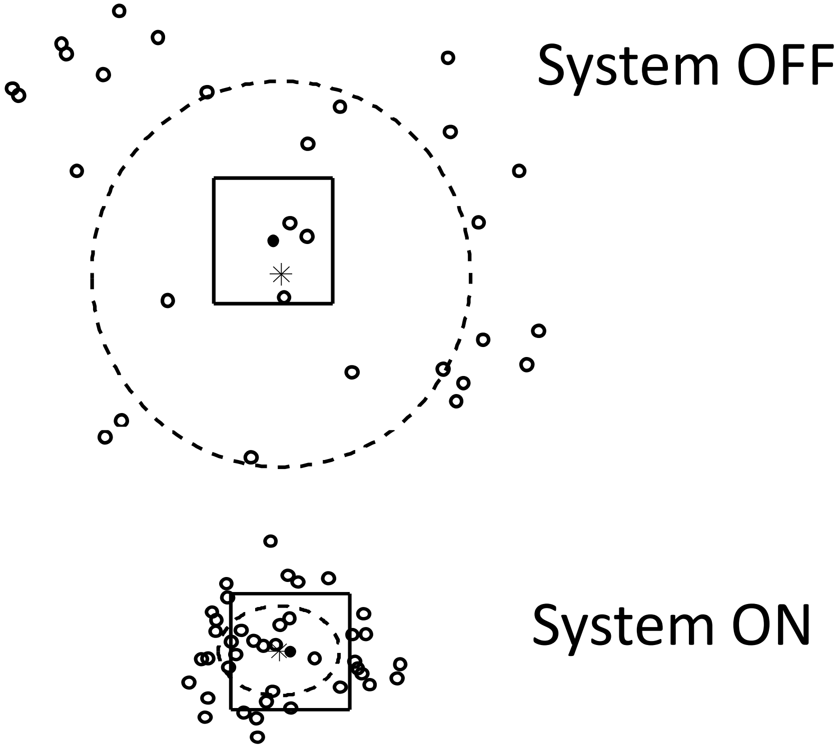
(Second Sight Medical Prodcuts, Inc.)

- EU and FDA approval
- 6x10 micro-fabricated electrode array
  - Polymer substrate
  - High surface area platinum
- Improved mobility demonstrated in multi-center clinical trial (n=30)
- Letter reading in majority of subjects



Square Localization in Argus II Patients



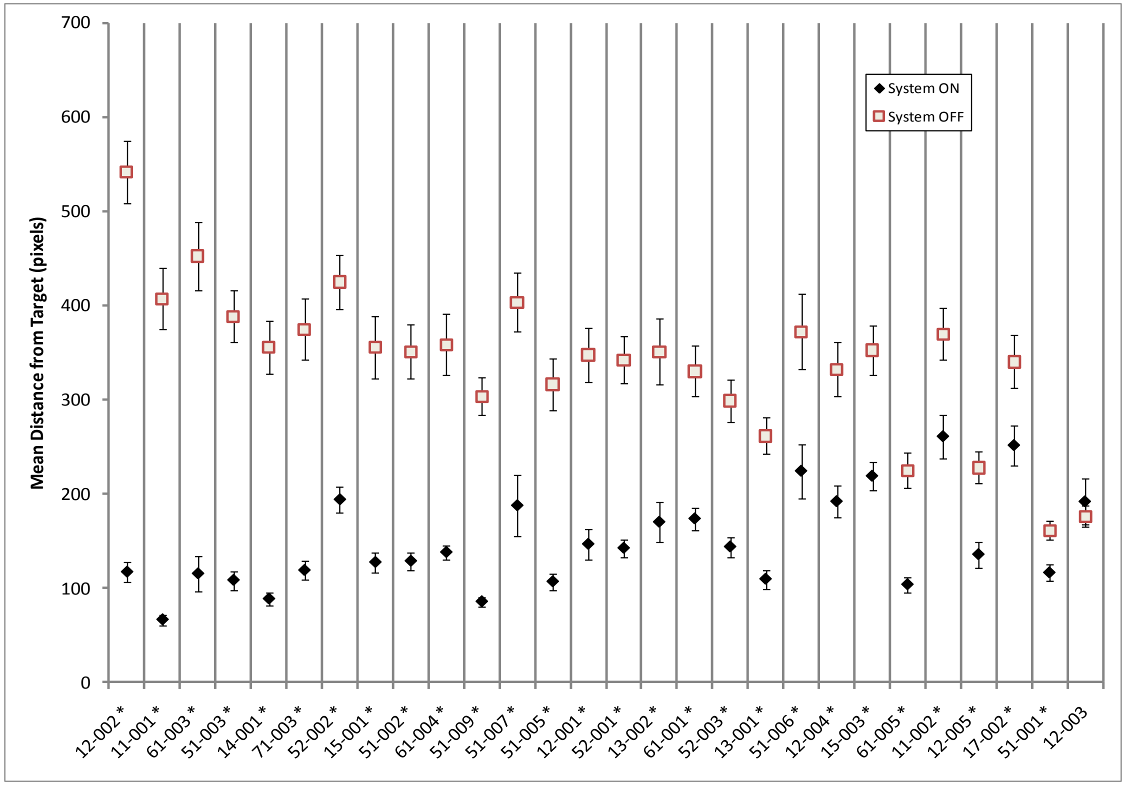


sample data from USC-001

- Square is 2.8” X 2.8”
- 40 trials System ON
- 40 trials System OFF, natural viewing

Square Localization Results

As of Last Follow-Up

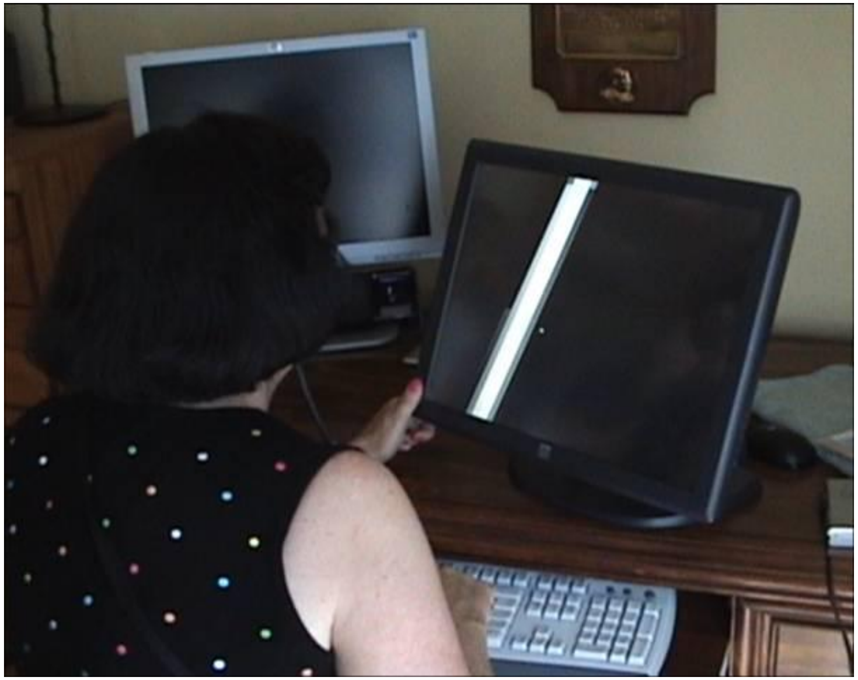


Compare the mean distance from the center of the target for the two conditions

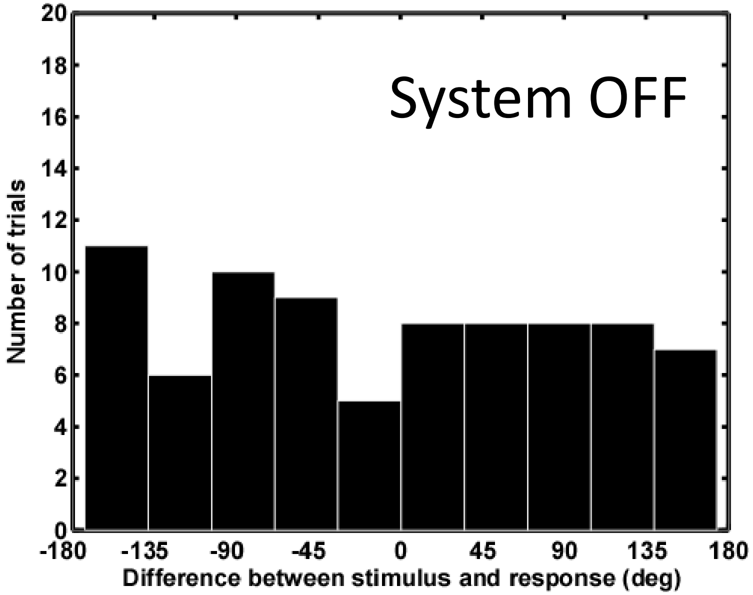
★= significant difference between the means

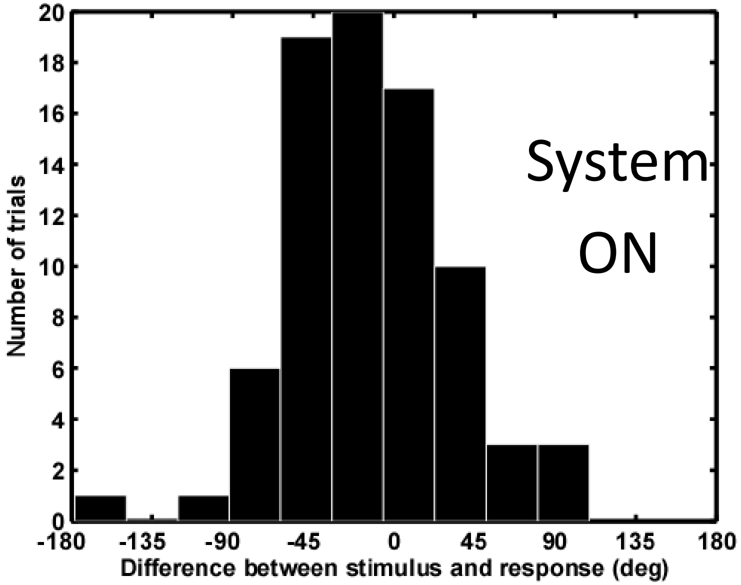
27 out of 28 subjects (96%) perform better with the System ON vs. OFF

Direction of Motion



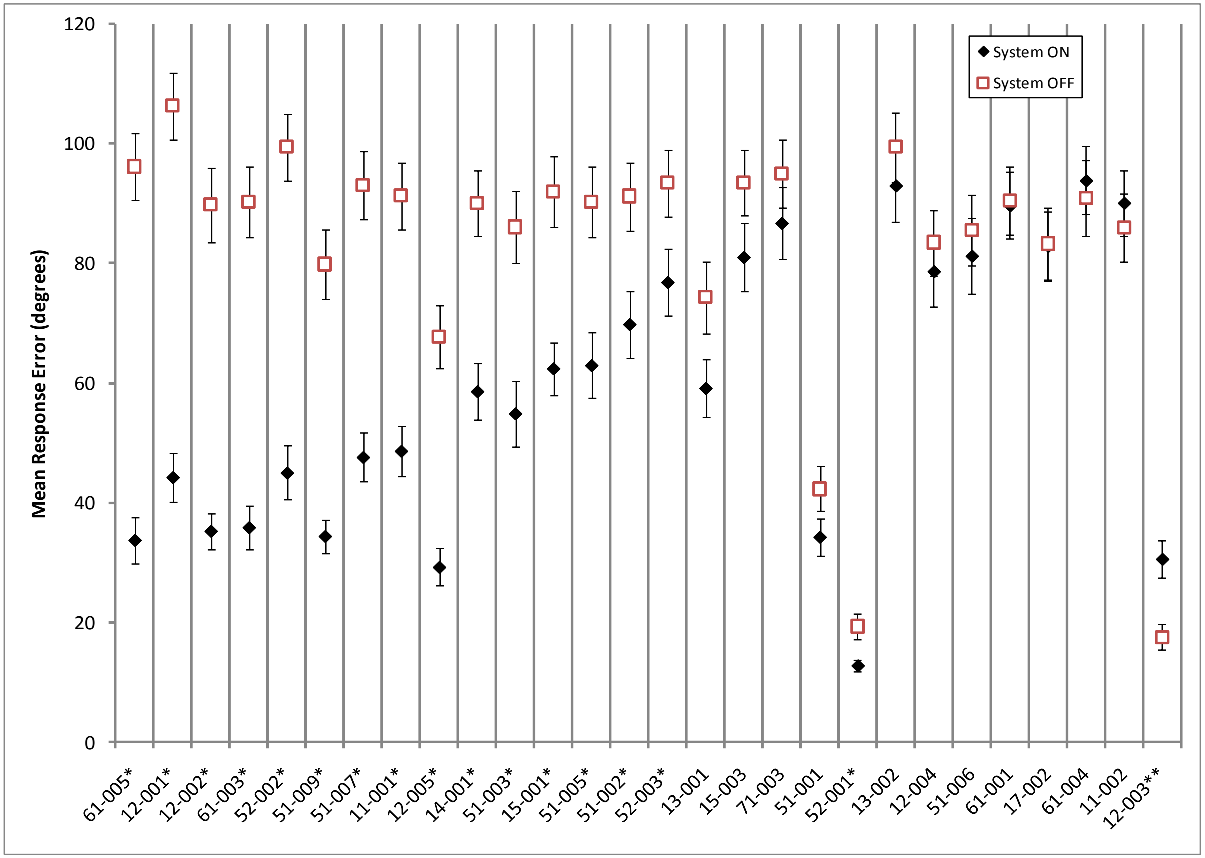
- Target bar is 1.4” wide, speed is chosen based on the subject’s preference
- 80 trials System ON
- 80 trials System OFF, natural viewing





Sample data from JHU-002

Direction of Motion Results
As of Last Follow-Up

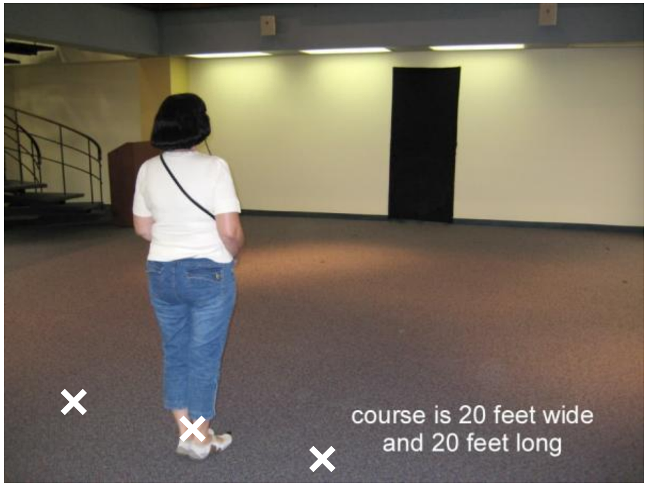


Compare the error distributions for the two conditions (target-response direction)
★= significant difference between the means

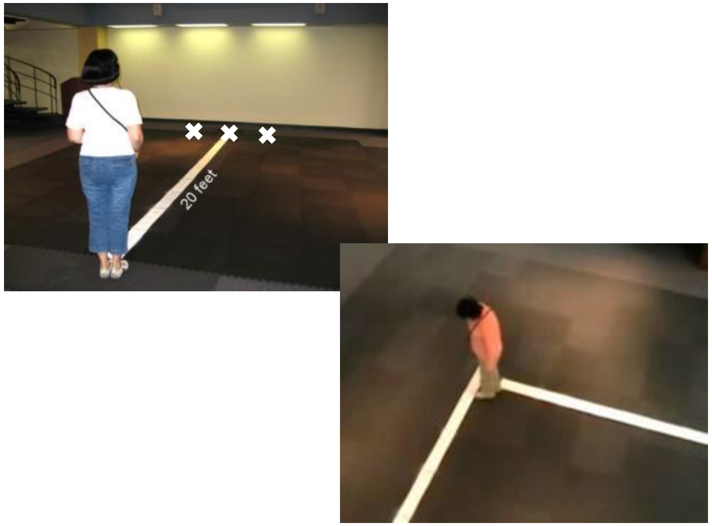
16 out of 28 subjects (57%) perform this test better with System ON vs. OFF
1 subject performs it better with the System OFF vs. ON

Orientation & Mobility

Door Task

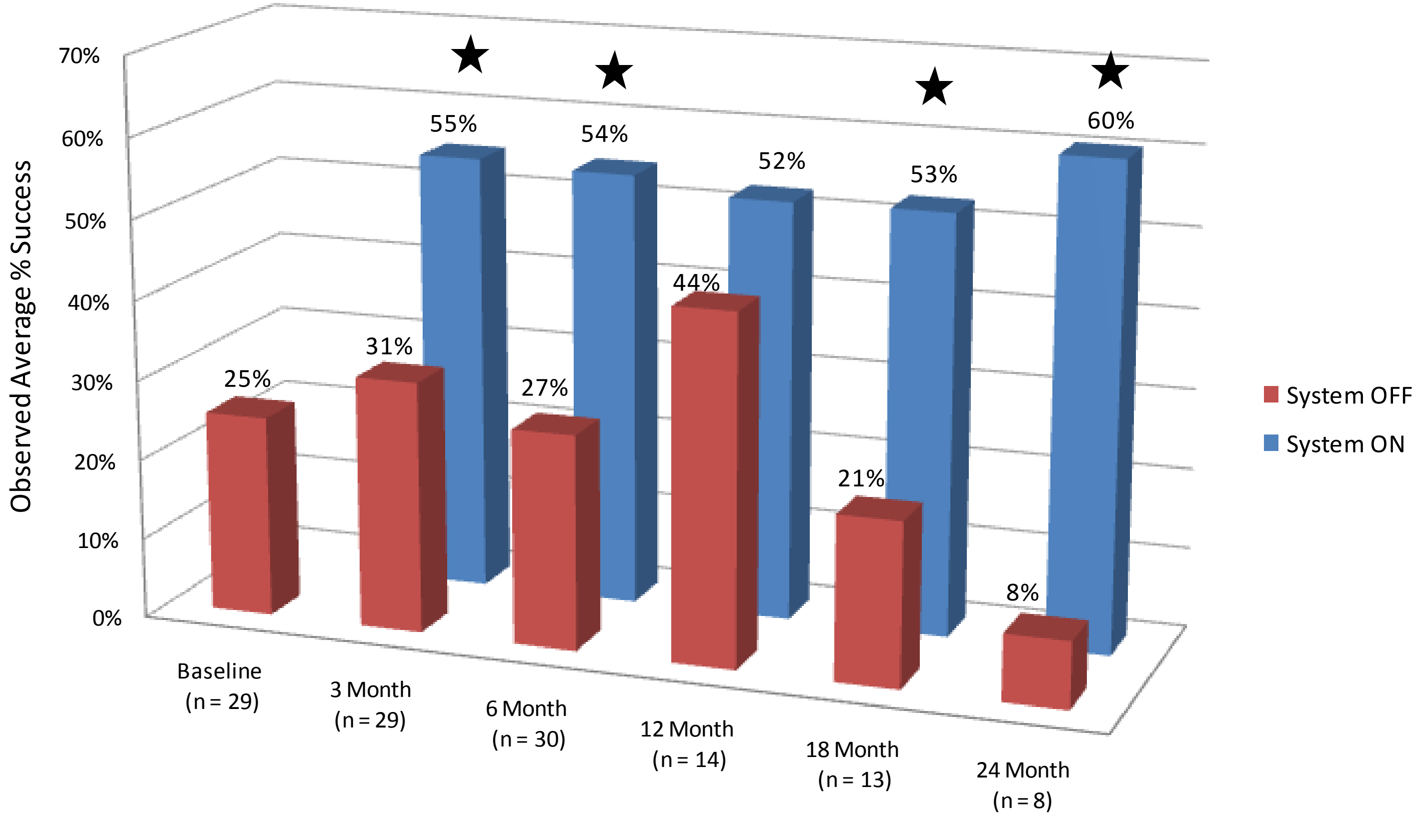


Line Task



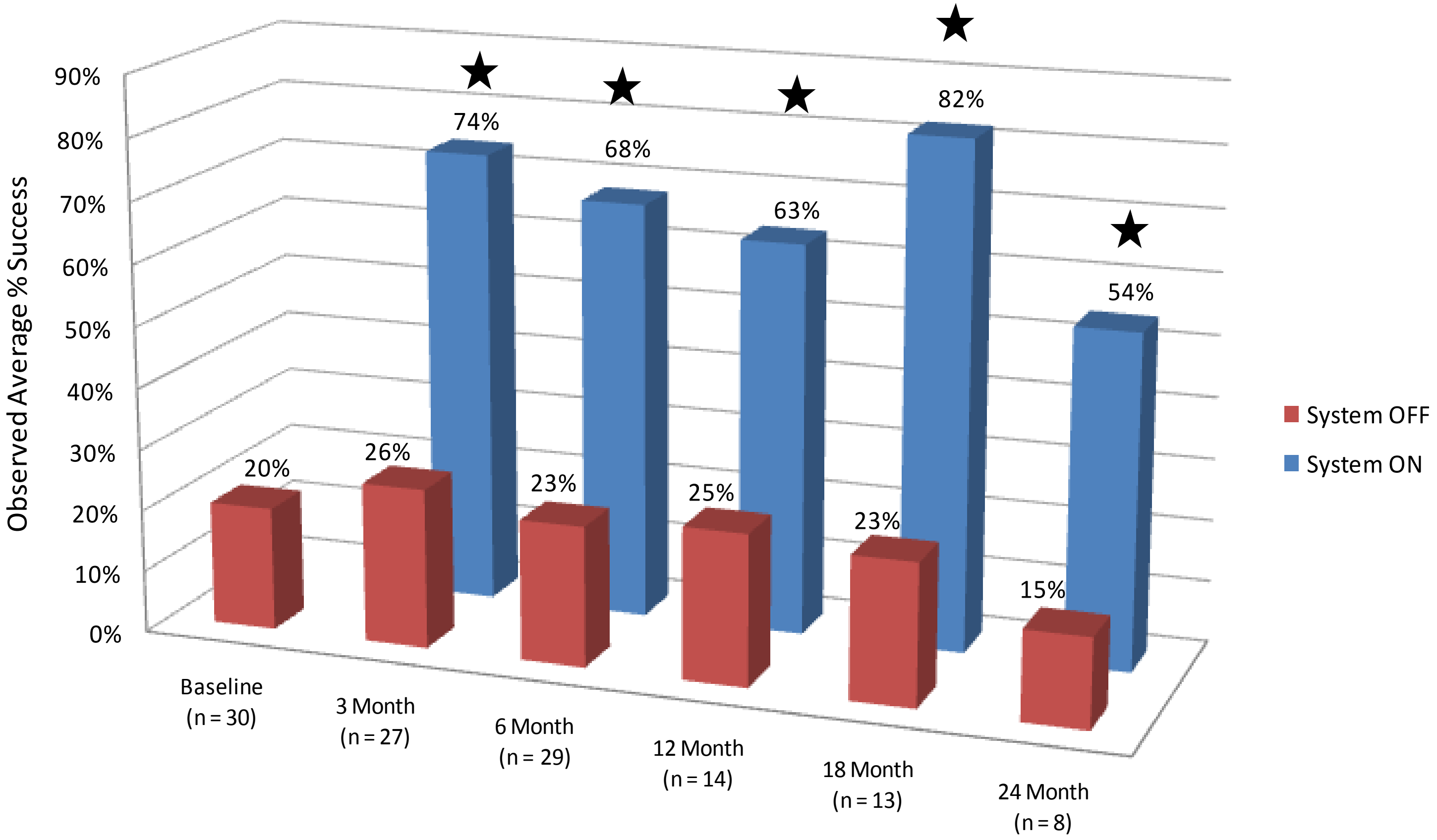
- 6 trials ON and 6 trials OFF. All tests performed binocularly.
- Success = touching the door or ending the course on the line

Door Test



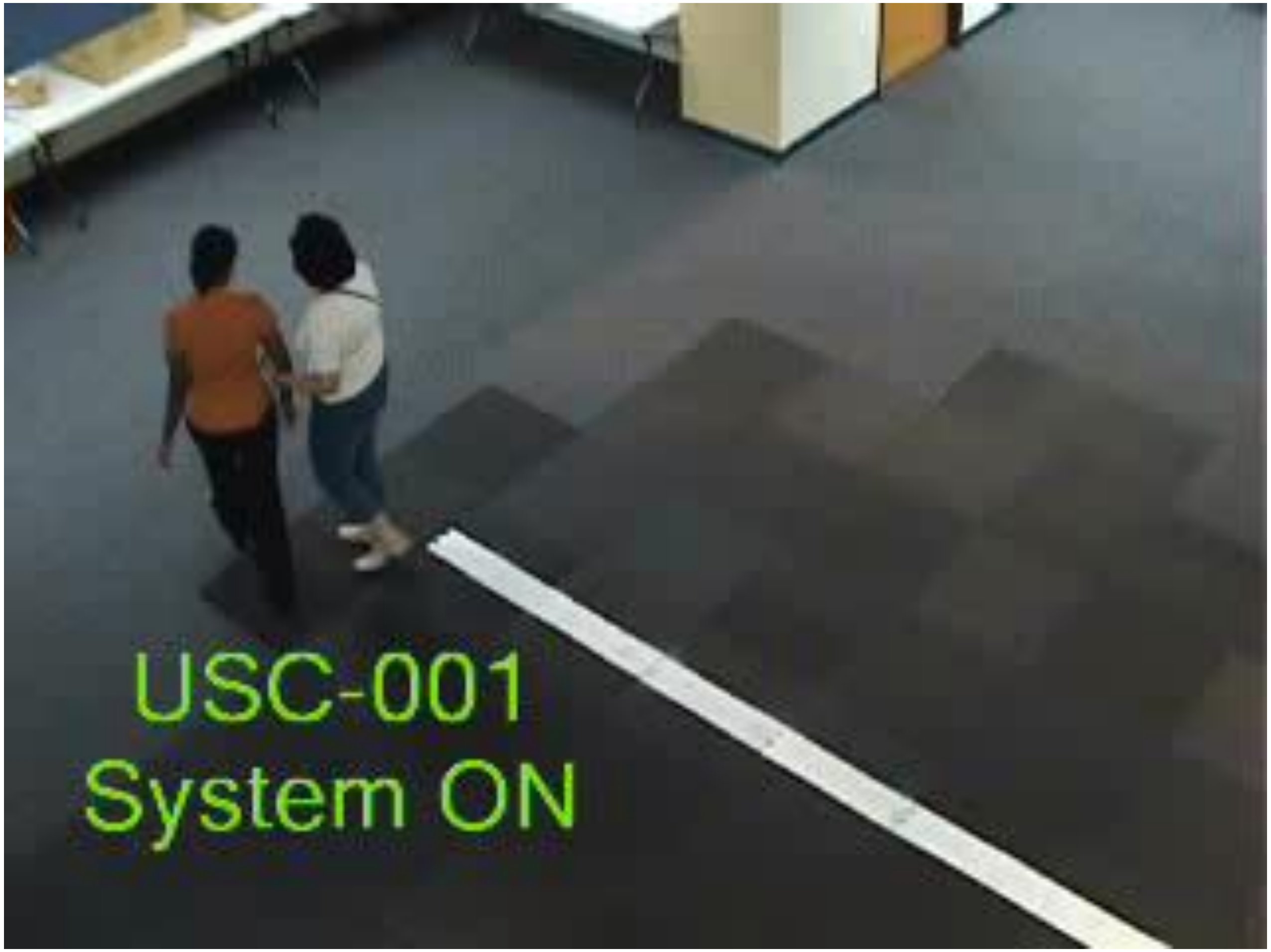
★ $p<0.05$ (Repeated measures analysis of variance [RM ANOVA])

Line Test



★ p<0.05 (RM ANOVA)

Mobility Testing



Letter Reading

Retinal Prosthesis Summary

- Multiple clinical trials show potential for partial sight restoration
- Safety of electrical stimulation and implantation is adequate
- Current focus is on optimizing existing devices and creating new technology for next generation devices

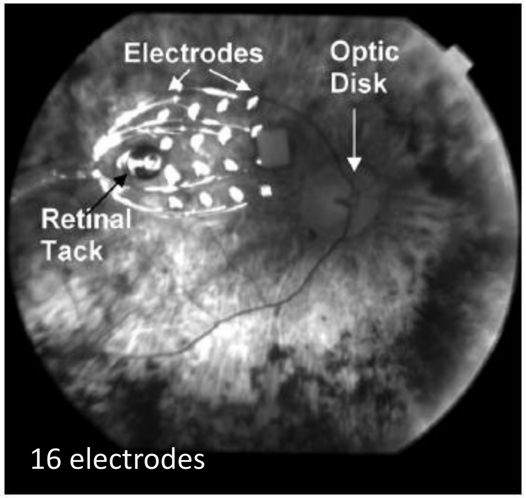
Spin-off Products

- Knowledge gained in implantable electronic systems was used to create spin-off products, two examples will be discussed
  - High-surface area Platinum-Iridium electrode materials for neural interfaces and sensing (Disclosure, I am part owner of Platinum Group Coatings, LLC)
  - Implantable drug pumps with electronic actuation (courtesy Ellis Meng)

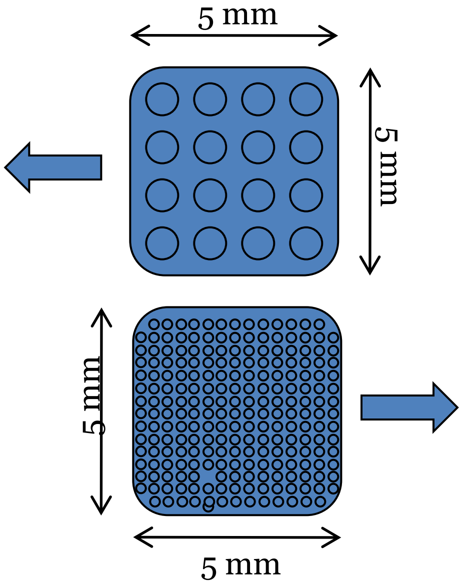
Platinum-Iridium (Pt-Ir) - Background

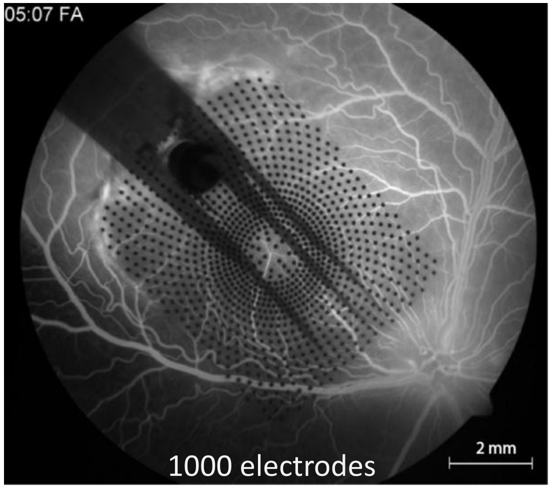
Efforts Towards High Resolution Retinal Prosthesis

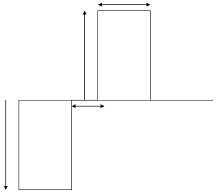
Simulation results predict 625-1000 pixels as a necessary condition for reading, face recognition

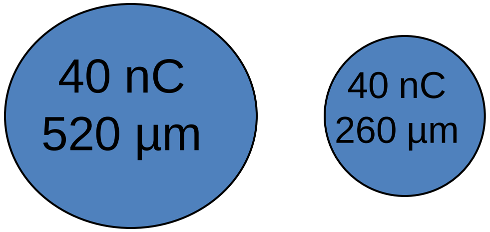


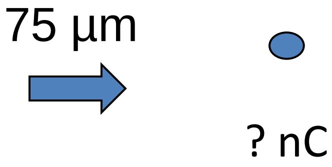
Mahadevappa et al. 2005











Pt-Ir Goals

-Develop electroplating process of high surface area Pt-Ir alloy

-Improved mechanical stability

- Improved charge injection limits

-Adhesion of electrodeposited material to the base electrode

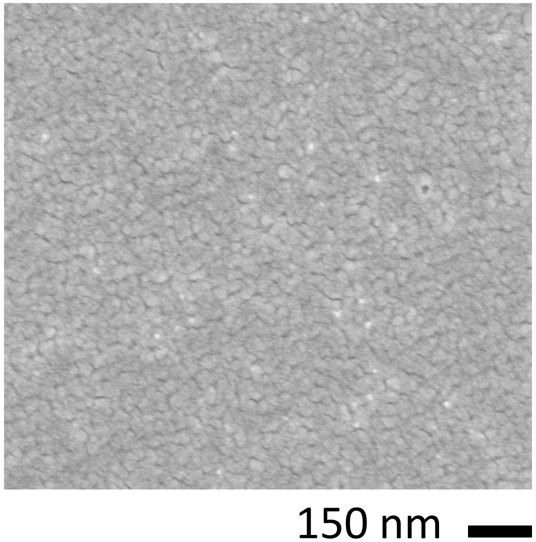
- Simple, reproducible, and scalable

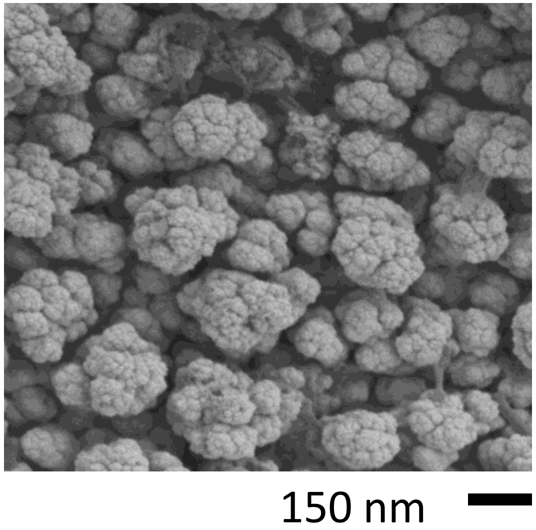
Pt-Ir Methods

Variables

- Electrodeposition technique
- Chemicals concentrations
- Electroplating bath temperature
- Sonication amplitude using ultrasonic homogenizer
- Optimum electroplating potential limits
- Electrodeposition rate

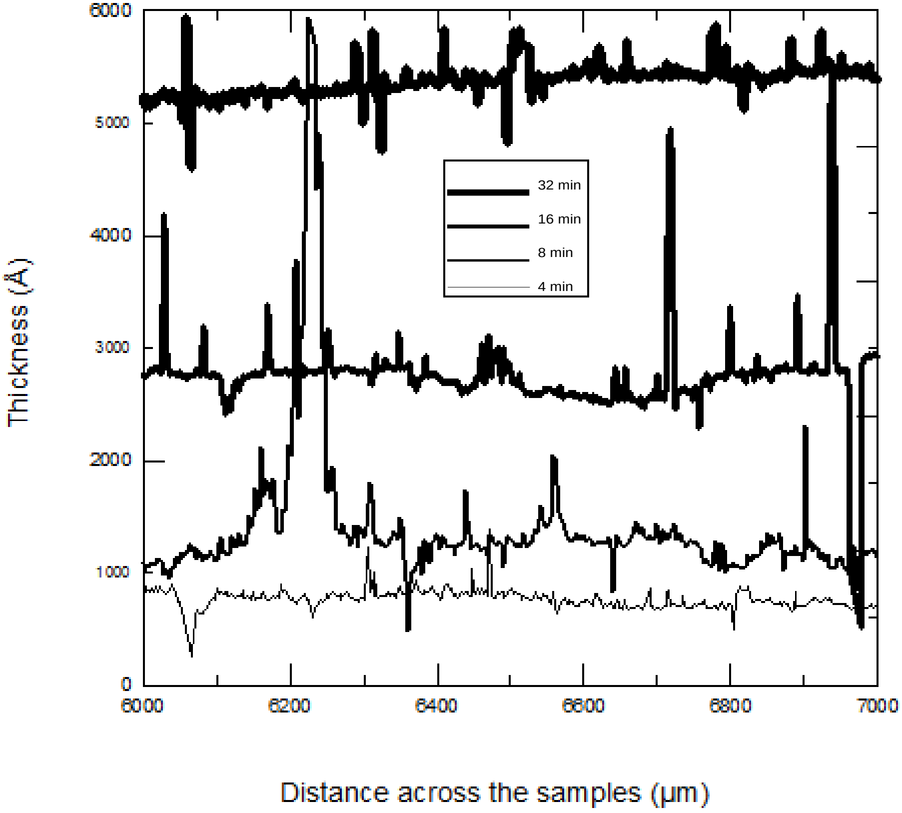
- Optimum combinations led to deposit 60-40% Pt-Ir films

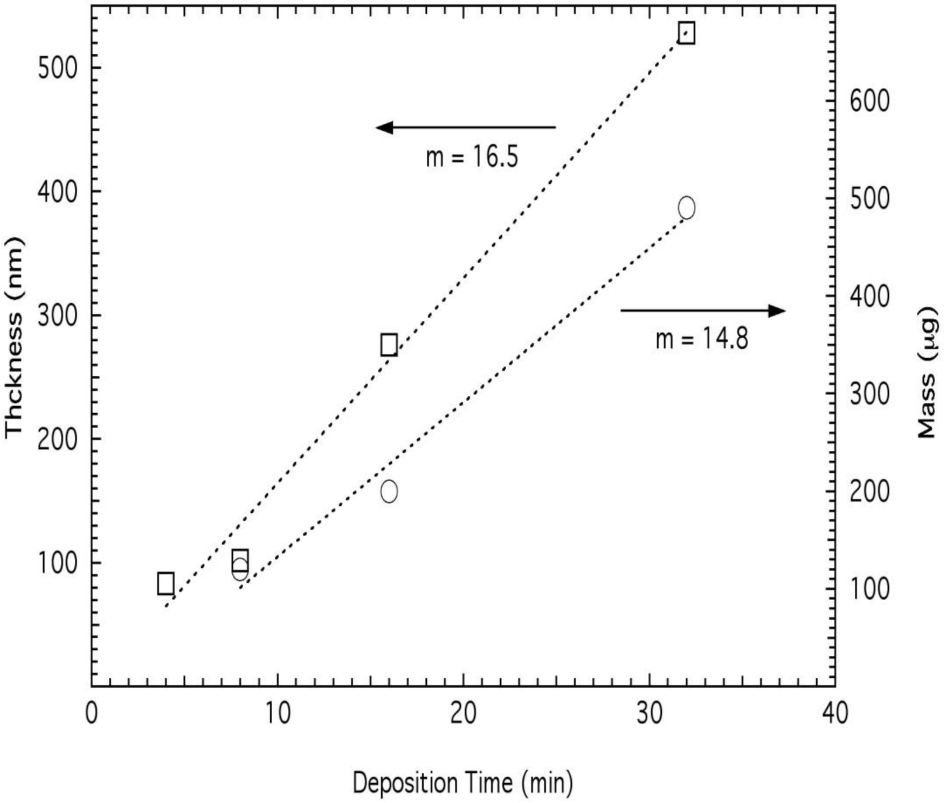




Pt-Ir Results

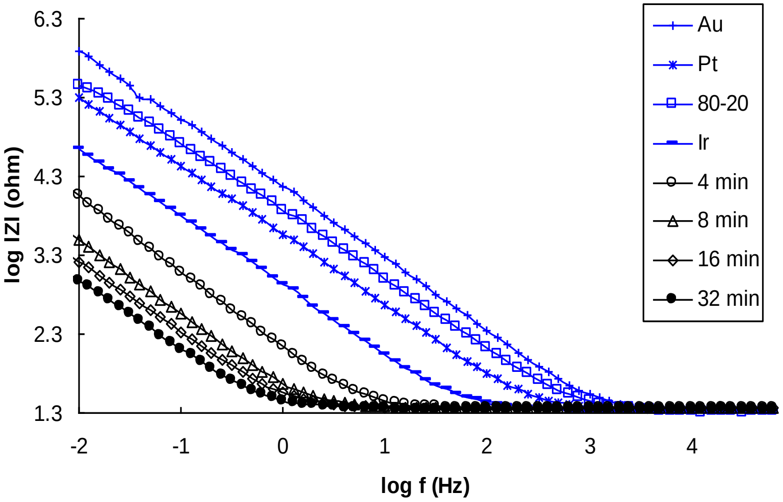
Mass and Thickness Measurements



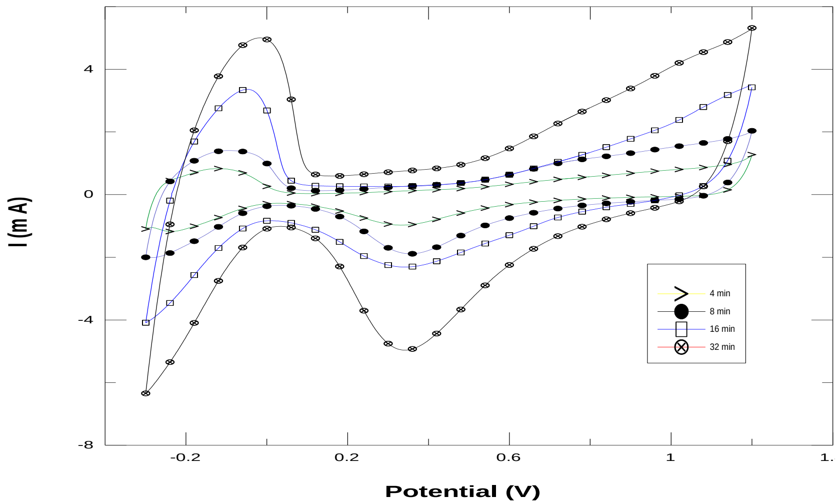


Pt-Ir Results

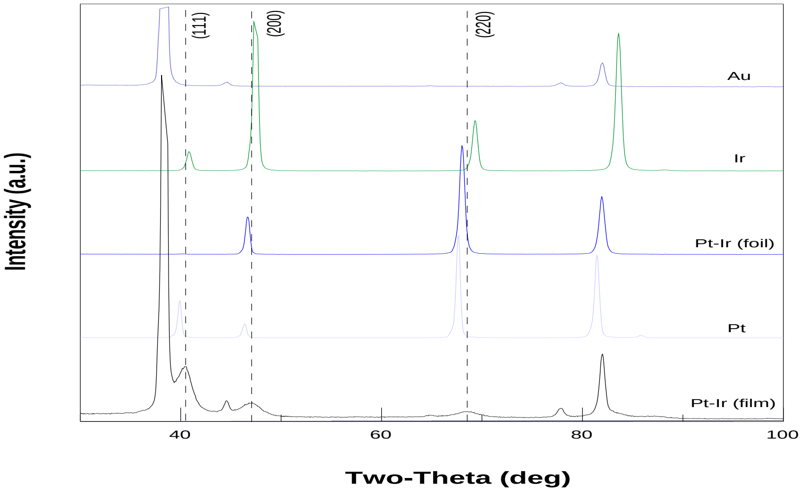
EIS



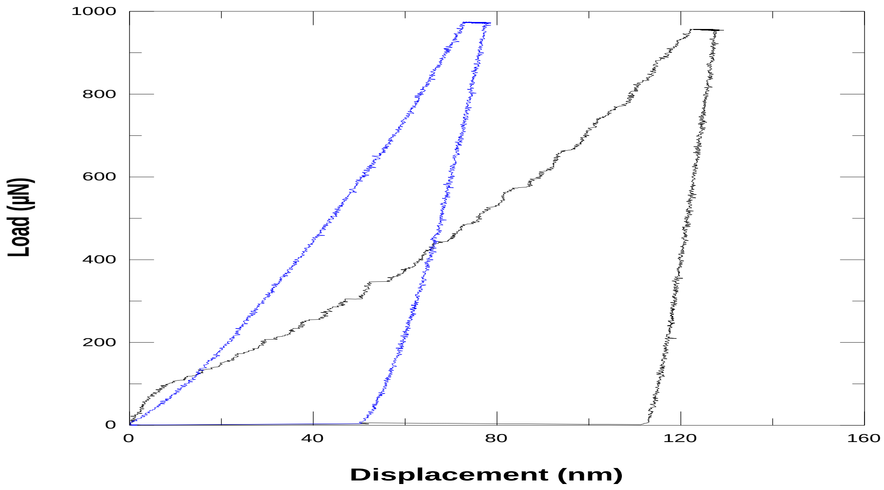
CV



XRD

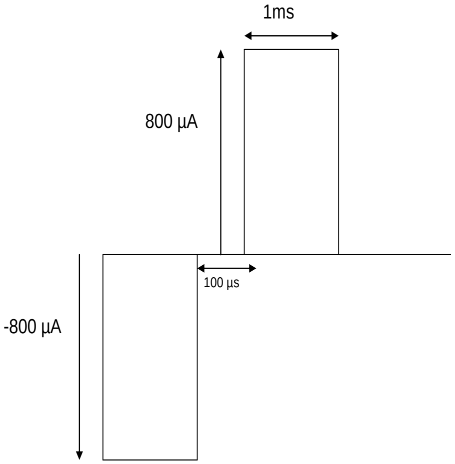


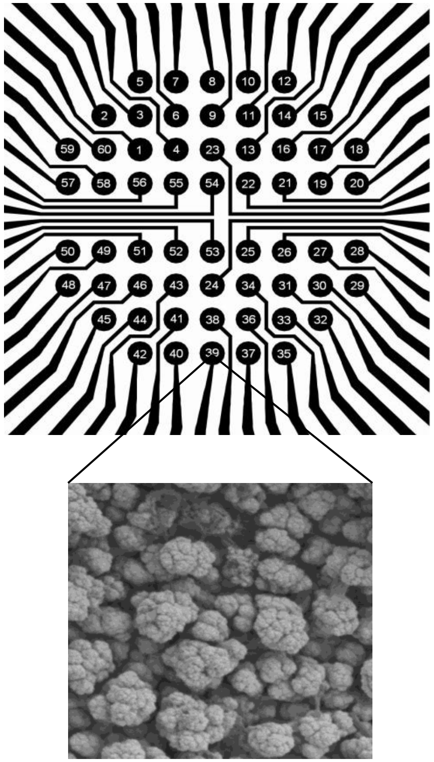
Nanoindentation

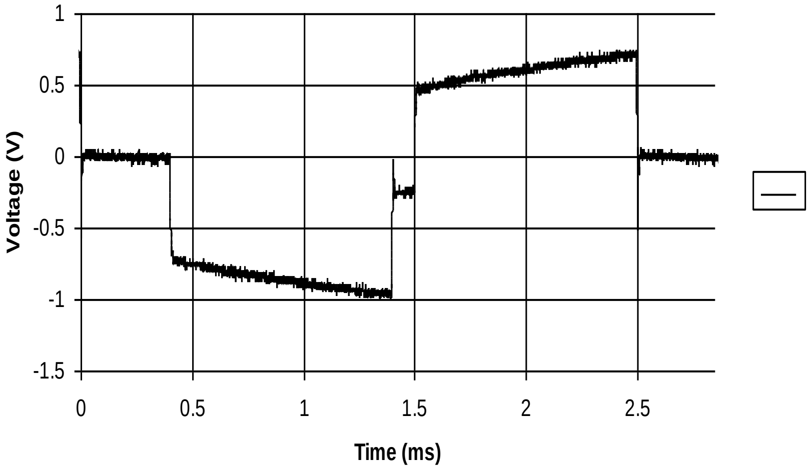


Pt-Ir Results

Voltage Response in PBS_Day 180







(24 hours (2X), 400 pps (20X)) :

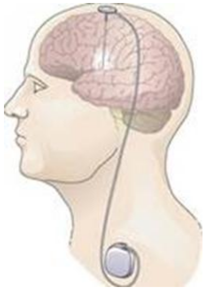
40X acceleration factor

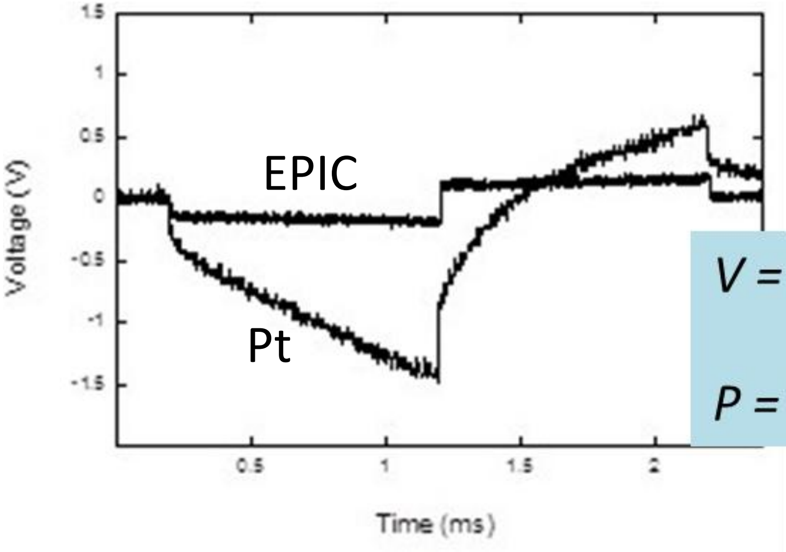
➡

7200 days of use in patient’s eye

2.5 mC/cm2 charge density

Application to DBS Electrodes



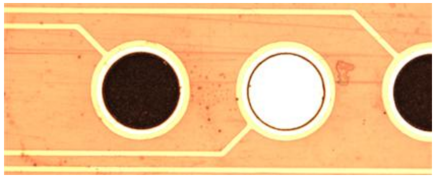


$V = I*R$

$P = V*I$

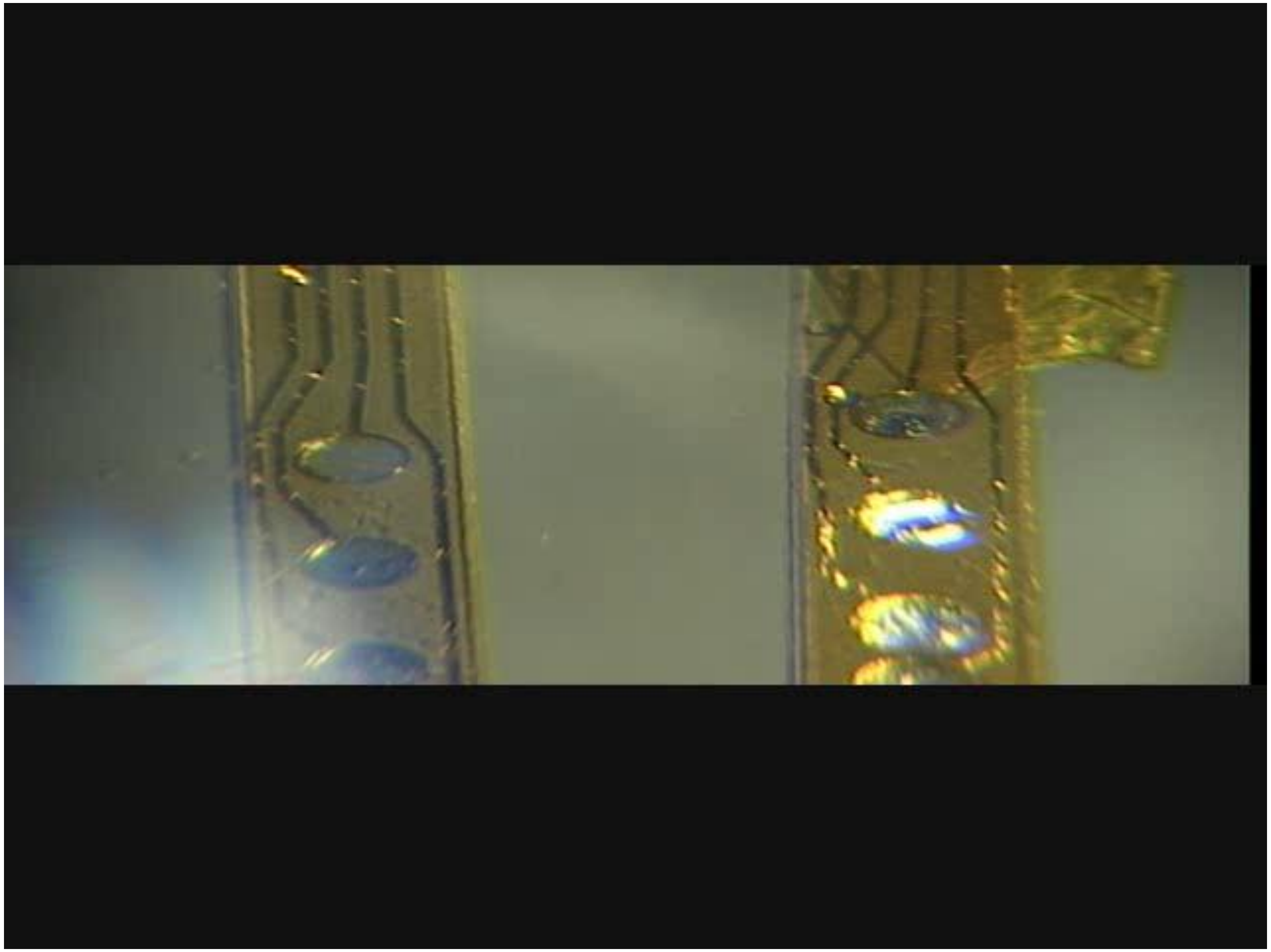
Current DBS Electrode
3 mm Cylinder

Concept Design for
Next Gen DBS (NeuroNexus)



EPIC Material on uFab Electrode

Photolithographic electrodes are robust with Pt-Ir coating

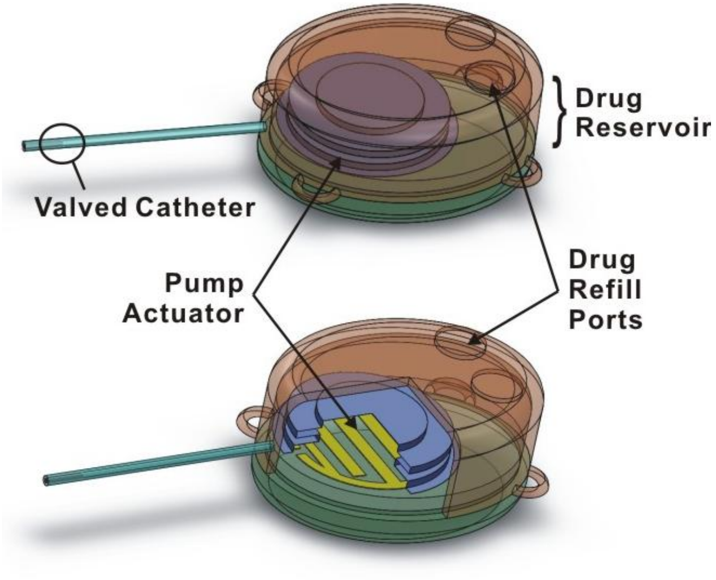


Pt-Ir Summary

- Need for better electrode material in retinal prosthesis resulted in high surface area Pt-Ir deposition process
- Applicable to any neuromodulation system
- Also applicable to neural recording and electrochemical sensing

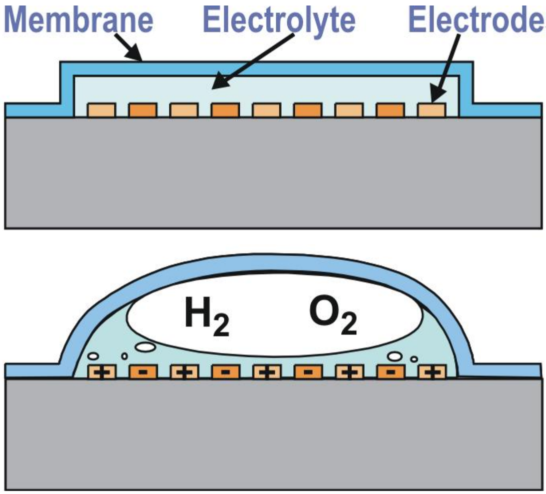
Implantable Electronic Drug Pump

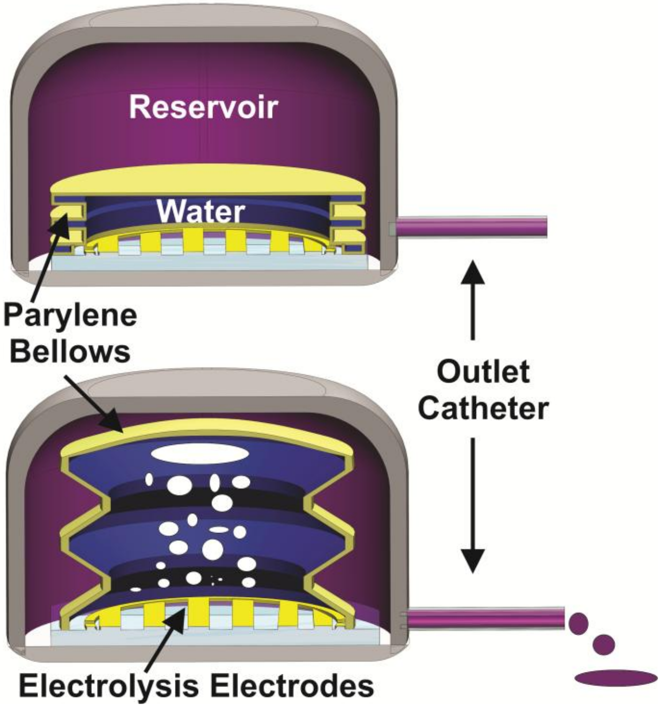
- Many diseases amenable to drug treatment
- Systemic delivery inefficient, may be harmful
- Passive drug delivery cannot adapt to different conditions



Electrochemical actuation

- Electrolysis actuation
  - Large displacement or volume change
  - Low power consumption (μW-mW)
  - Negligible heat production
- Simple design
  - Interdigitated electrodes
  - Electrolyte





Microtechnology-enabled drug infusion pumps

MEMS enabled micropump

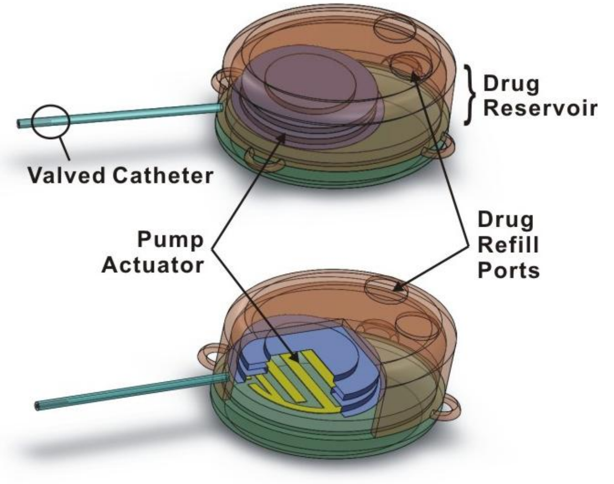
- Electrolysis actuator
- Refillable reservoir with flexible cannula
- Microfluidic flow regulation and valving
- Integrated sensors

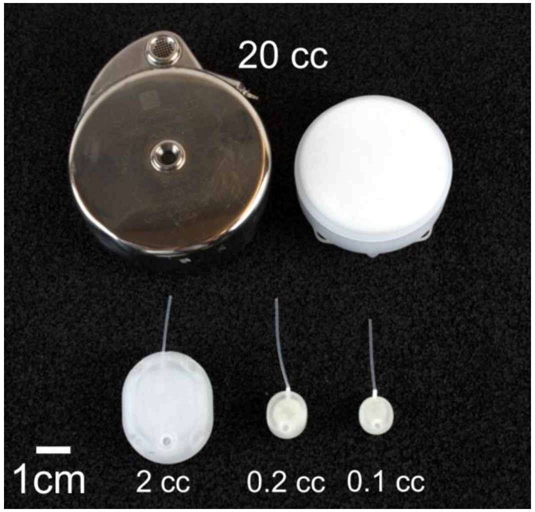
Unique implantable device design

- Small form factor
- Refillable drug reservoir
- Wireless power & connectivity

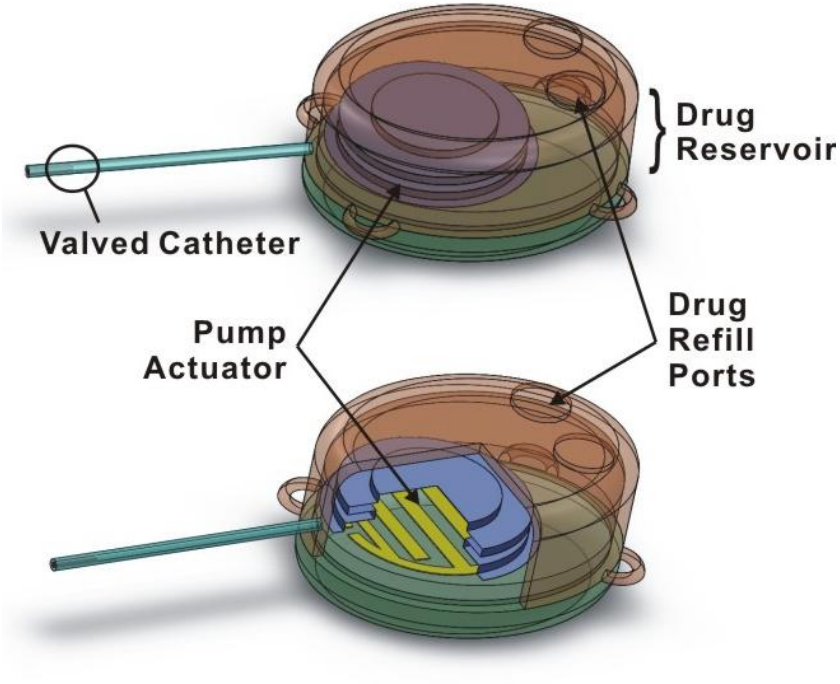
Superior pump mechanism

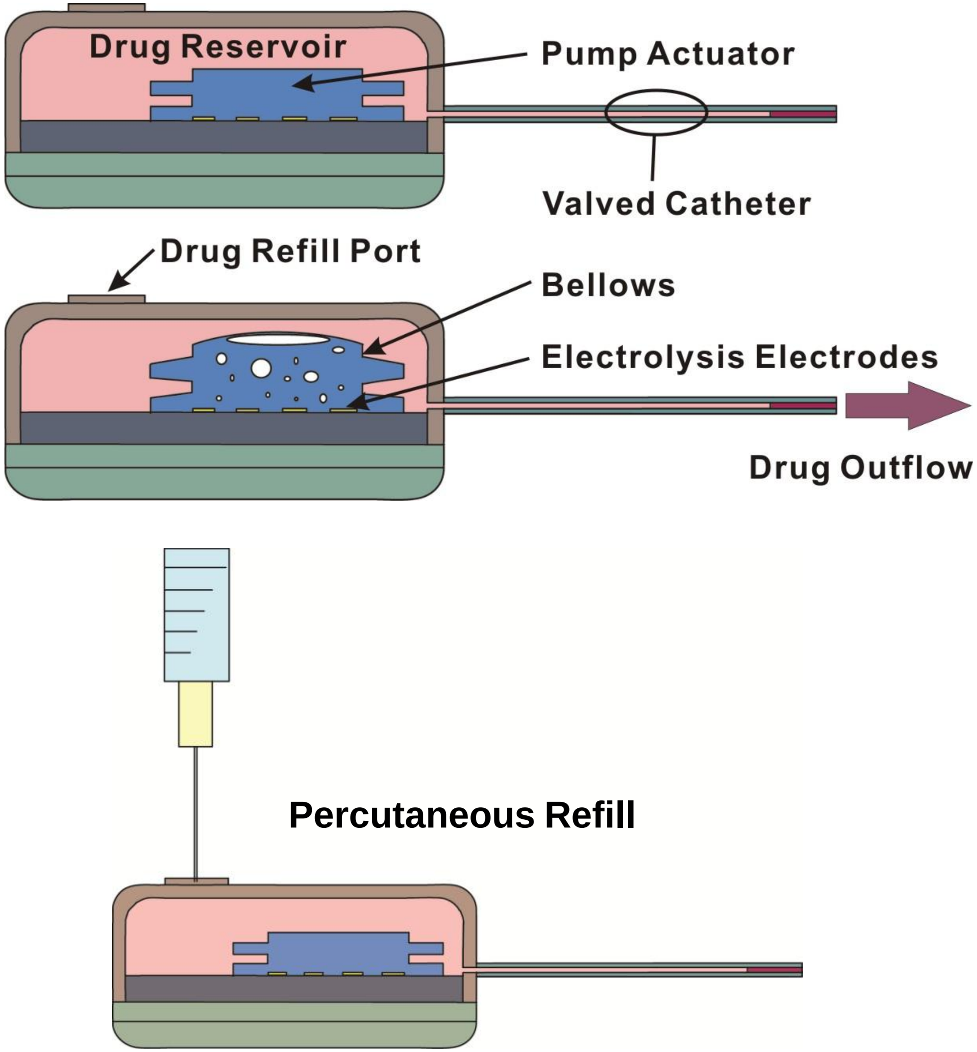
- High accuracy
- Adjustable dosing scheme
- Low power, low heat
- Scalable



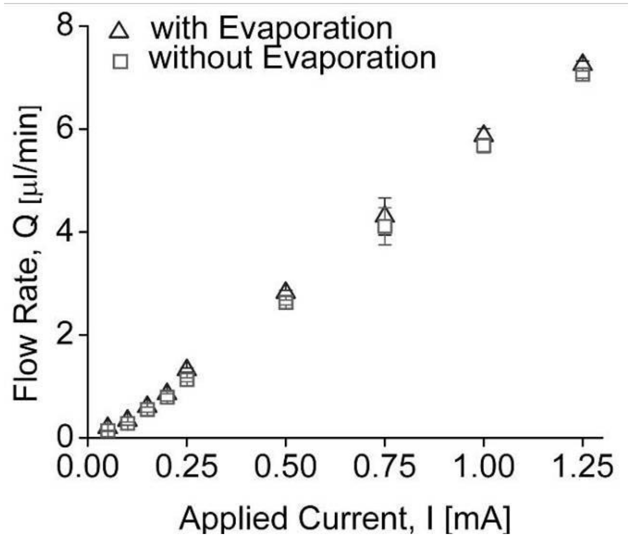


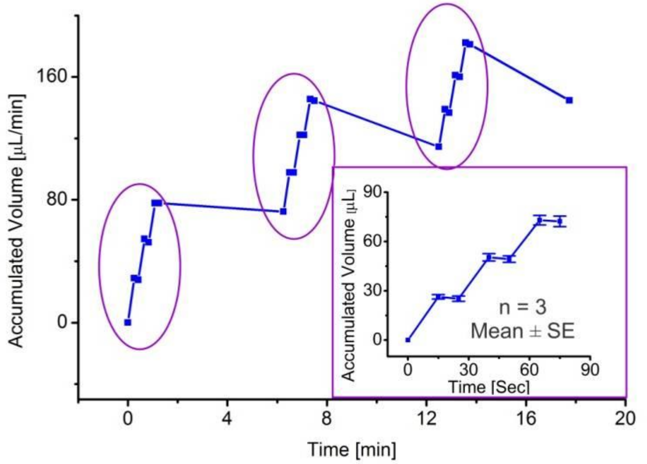
Electrolysis-based drug infusion

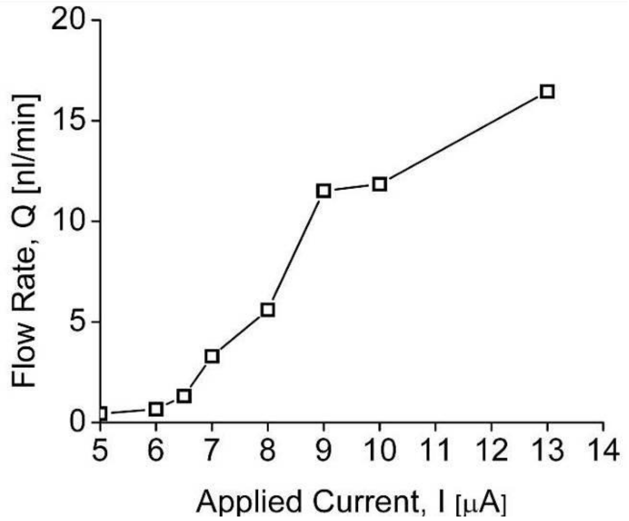


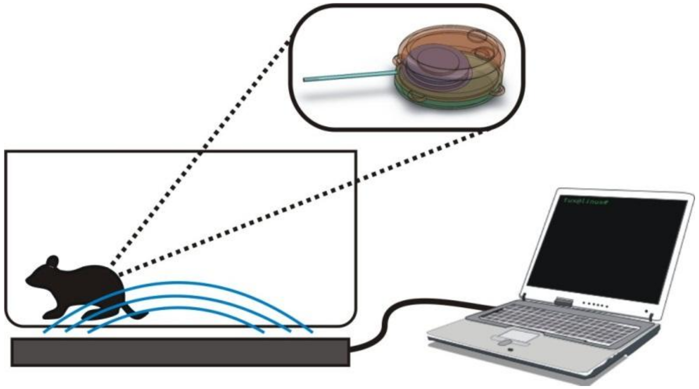


Electrolysis-driven pumping



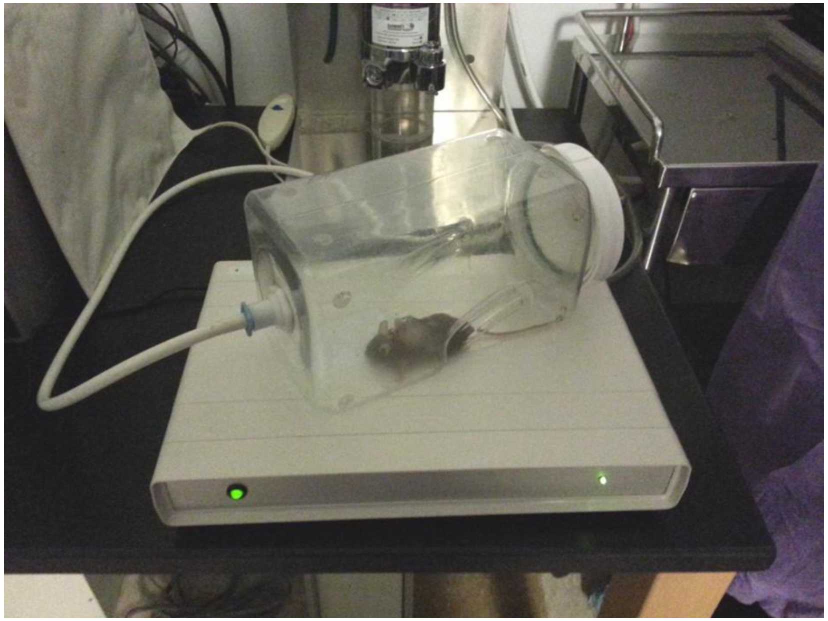






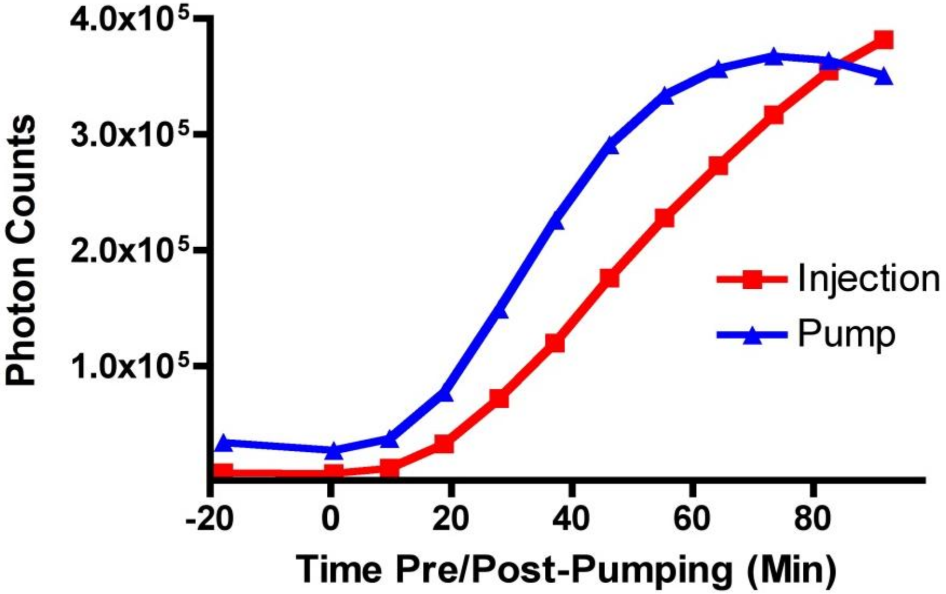
Subcutaneous implantation and wireless pump activation

(Left Top) Post-operative image of pump implanted over right shoulder.
(Left Bottom) Post-op image of incision where catheter entered the IP space.

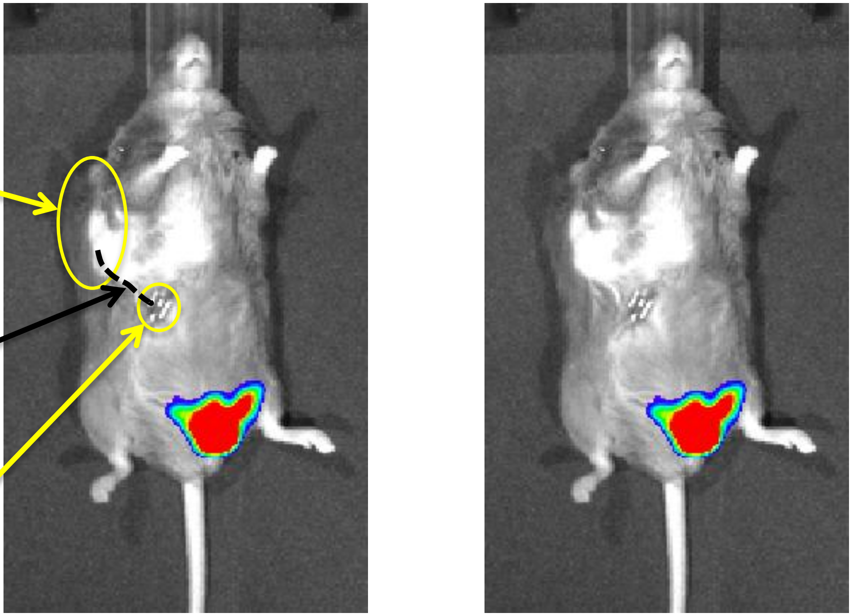


Anesthetized mouse on wireless base station for 9 minutes (30 μL dose) prior to imaging.

Time course of bioluminescence following IP infusion of luciferin



IP infusion of chemodrug + luciferin into luciferase-expressing transgenic mouse



Pump located on right upper back. White area is where fur was shaved.

Catheter route under skin. It extends another ~1.5 cm into the intraperitoneal space.

Skin staple at site of catheter entry into intraperitoneal space.

- Pump loaded with thiotepa (10 µg/30 µL) and luciferin (4.8 mg/mL)
- Pumping occurred for approximately 9 min (30 µL)
- Image taken at 55 mins (soon after the peak of bioluminescence at ~45 min) after the start of pumping

Summary

- Bioelectronic systems are currently used to treat neurological conditions such as deafness, movement disorders, and blindness, with varying degrees of effectiveness
- Next generation visual prostheses will require new technology to increase both the number and density of contacts with neural tissue
- Technology from next gen visual prosthesis can be applied to other implantable systems