# Assembly Development of a Highly Flexible and Biocompatible Optoelectronic Neural Stimulator for Implantable Retinal Prosthesis

Yu-Hsin Liu, Yi Jing, Brandon Bosse, Samir Damle,

Abraham Akinin, Sue Bauchner, Hiren D. Thacker

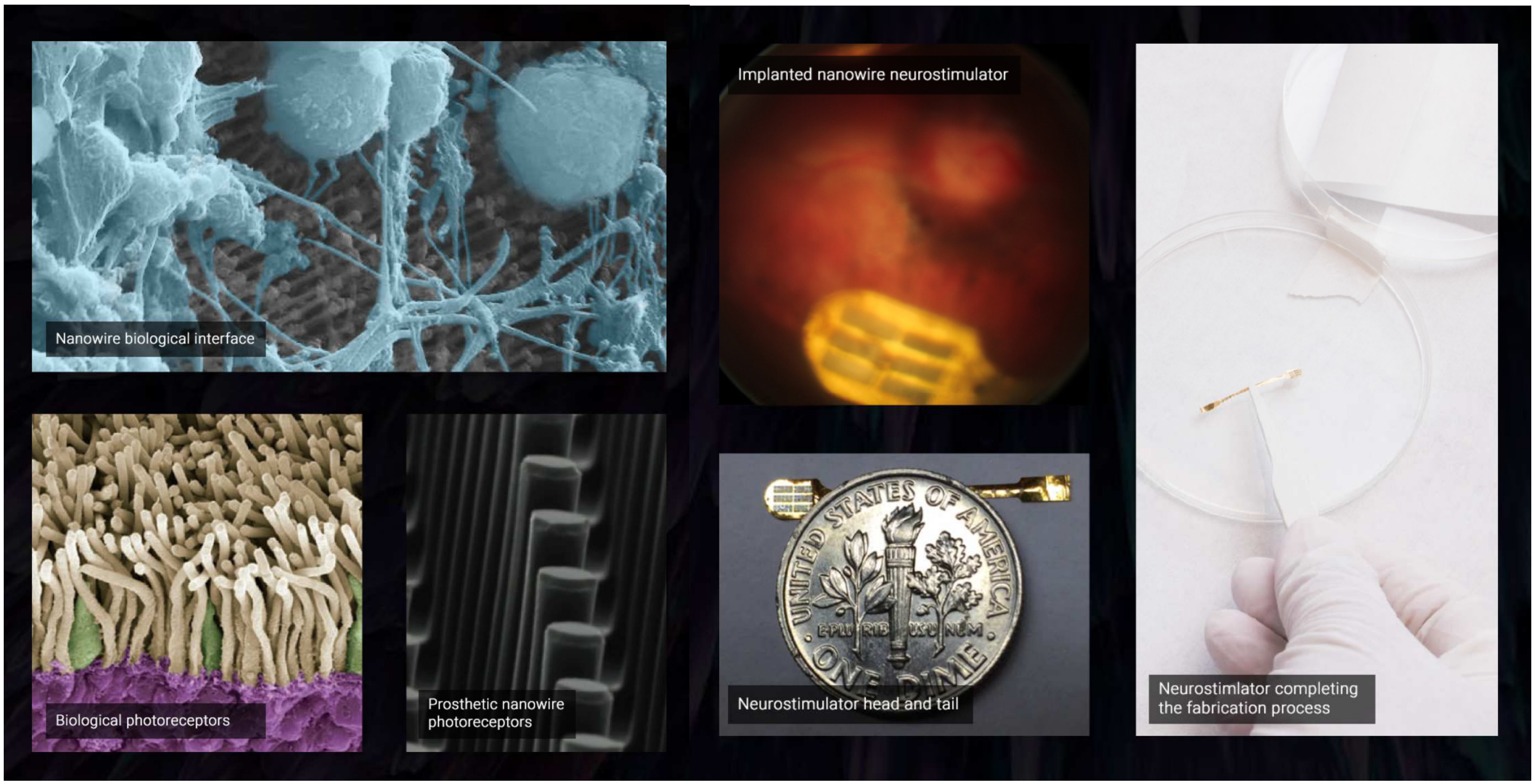
Nanovision Biosciences, Inc.
yuhsin@nanovisionbio.com



2021 IEEE EPS Silicon Valley Area Chapter

# Nanovision Biosciences

Advanced implantable sensor technologies that restore vision for those afflicted with incurable and degenerative retinal diseases



# Outline

- Introduction to Retinal Prosthesis
- Nanovision's Retinal Prosthesis
- Assembly of the Neural Stimulator
- Electrochemical Testing
- Reliability Testing → Accelerated Lifetime Testing
- Summary

# Degenerative Retinal Disorders

nanovision

*Age-related Macular Degeneration (AMD)*


Normal vision


Vision w/ AMD

- AMD is a disease that blurs the sharp, central vision needed for “straight-ahead” activities (reading, sewing, and driving).
- AMD affects the macula, the part of the eye that allows you to see fine detail.
- 11 million in the USA, 22 million by 2050[1]

*Retinitis Pigmentosa (RP)*

Normal vision

Vision w/ RP

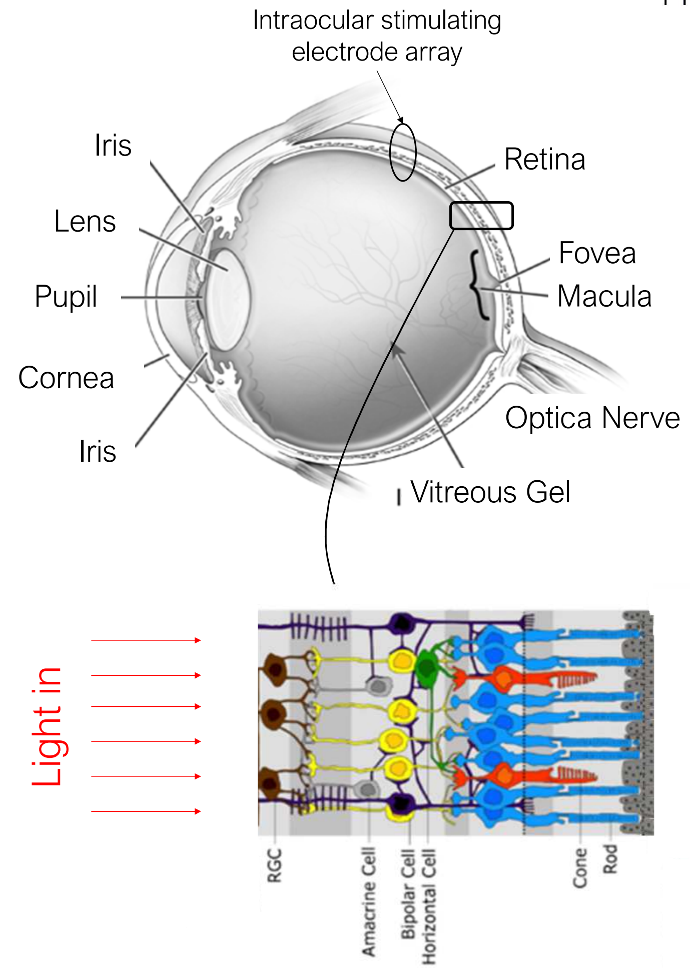
- Retinitis pigmentosa (RP) is a group of rare, genetic disorders that involve a breakdown and loss of cells in the retina.
- Common symptoms include difficulty seeing at night and a loss of side (peripheral) vision.
- 100,000 in the US, 1.5 million worldwide[2]

*Currently no prosthesis or treatment available to restore high visual acuity for advanced stages of retinal diseases with significant loss of photoreceptors*

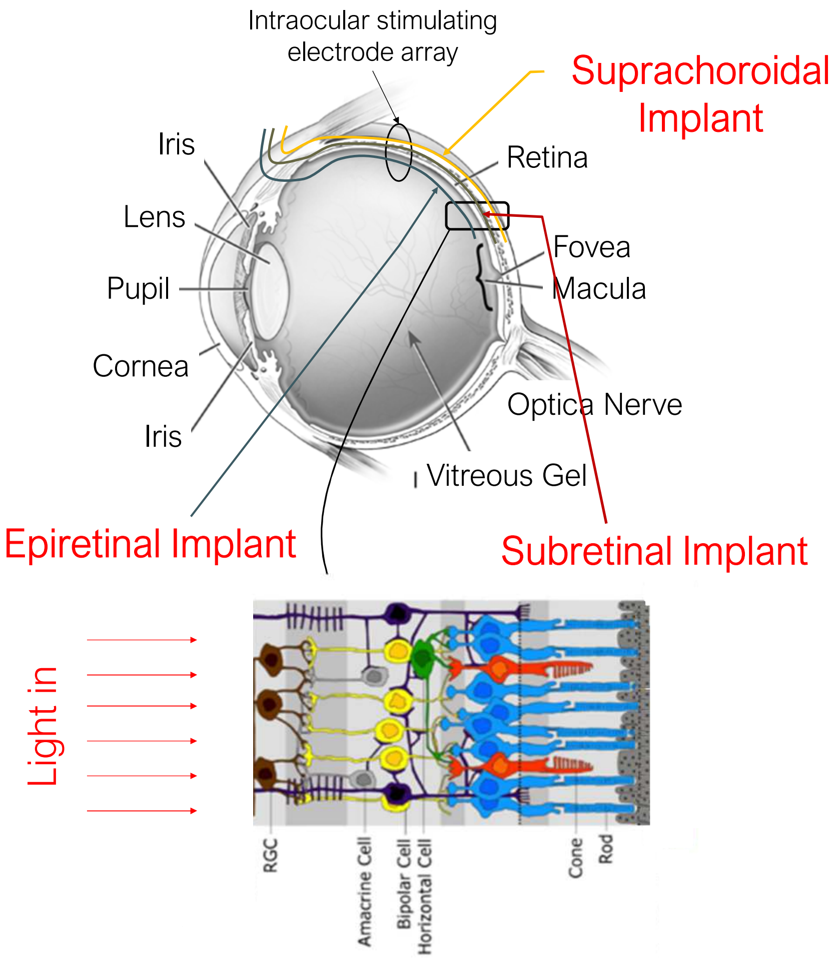
[1] Bright Focus Foundation, www.brightfocus.org [2] Foundation Fighting Blindness, www.blindness.org

# Retinal Prosthesis

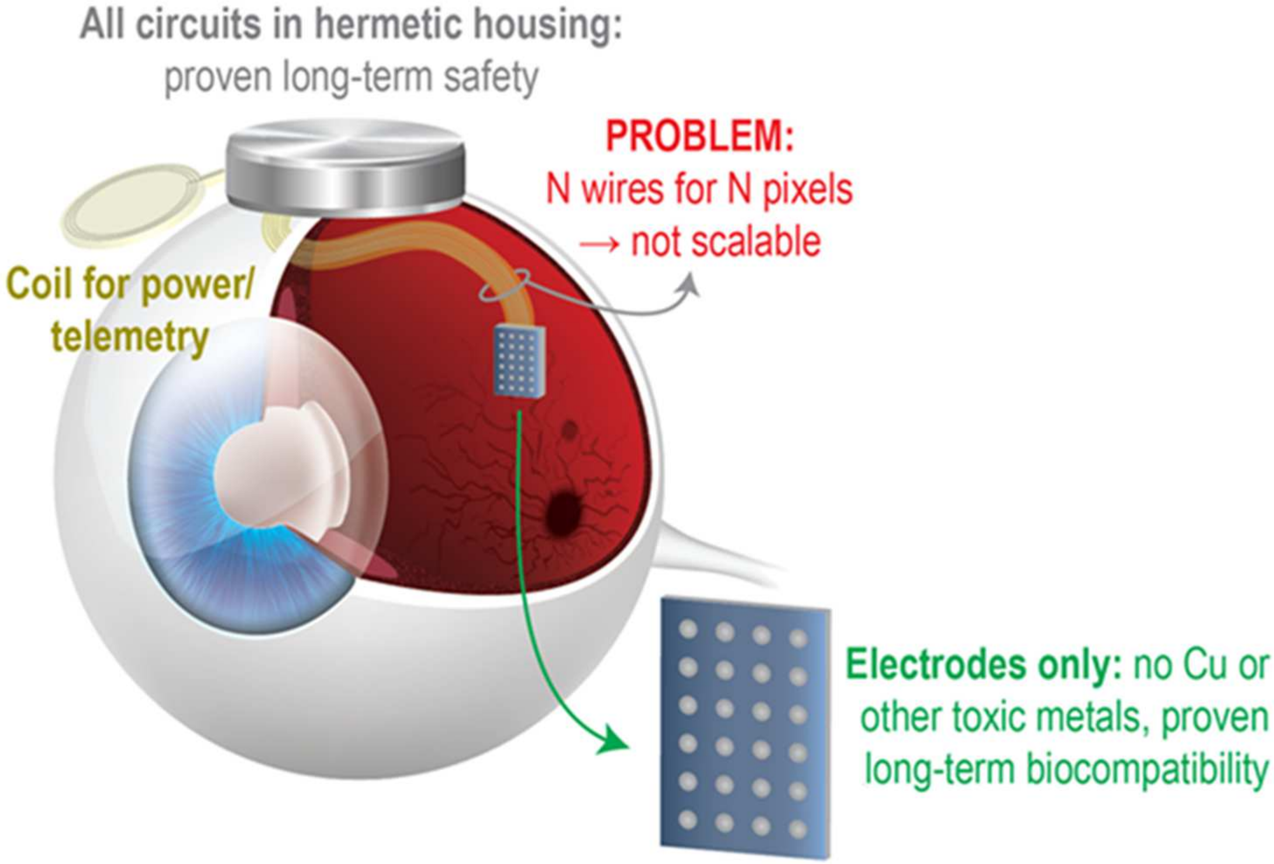
- A retinal prosthesis device places an electrode array in close proximity to the retina
- Even with advanced photoreceptor degeneration in these conditions, the neural circuits are functional
  - Ganglion cell density does not differ from that in normal eyes – even when 0 photoreceptors remain
- Charge injected beyond a threshold initiates firing of action potentials resulting in a visual percept



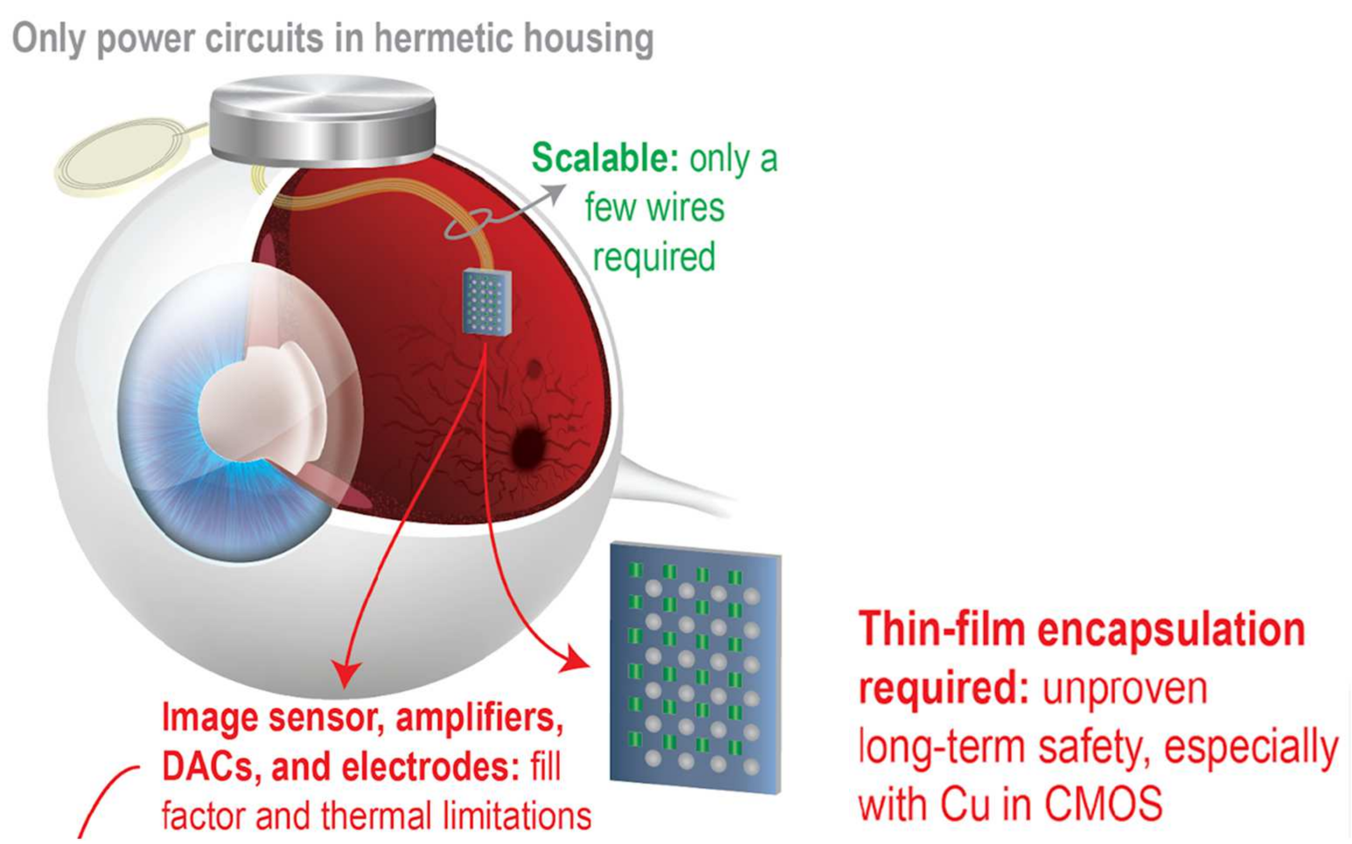
# Implant Location



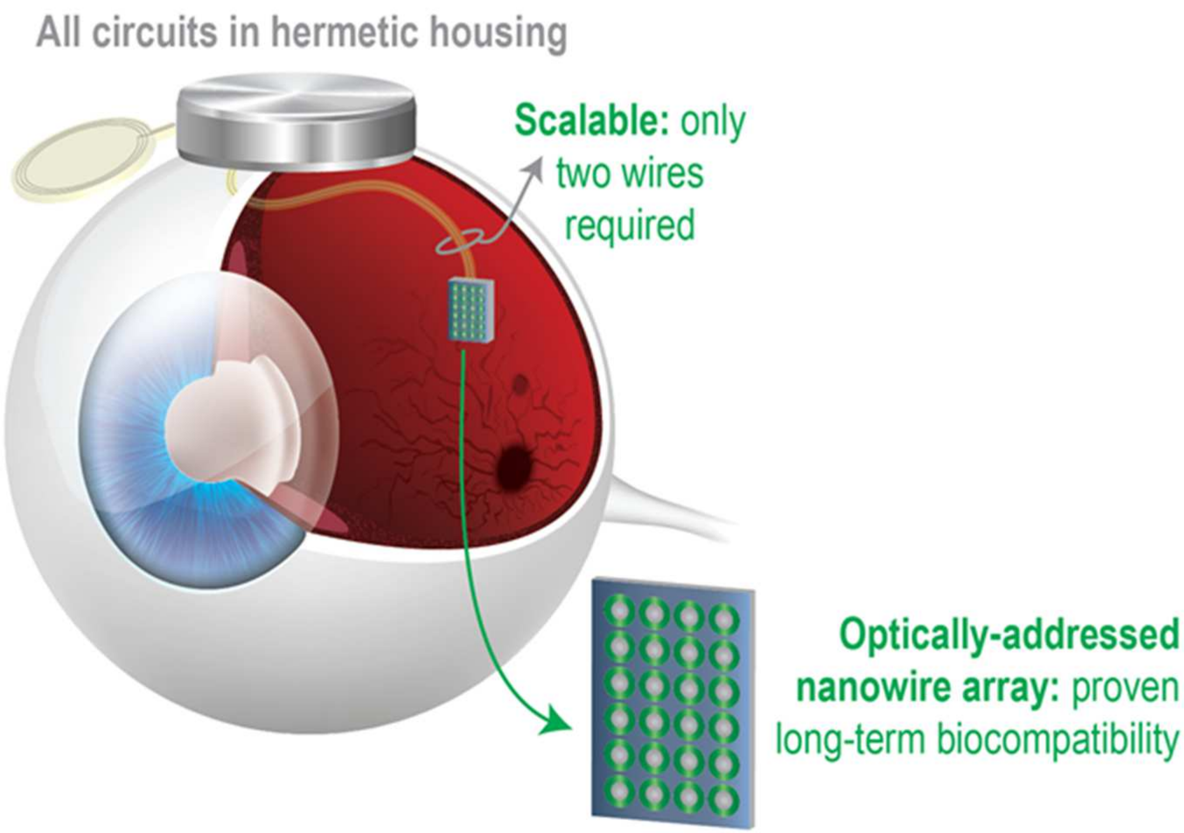
# Current Clinical Practice



# Emerging Approach

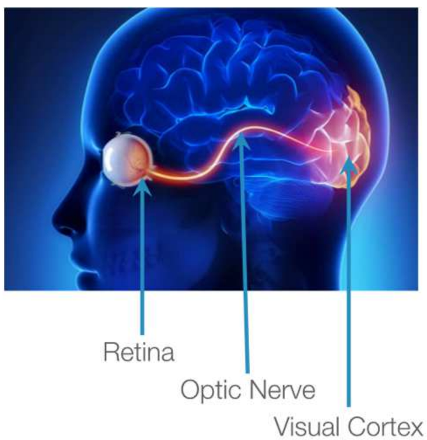


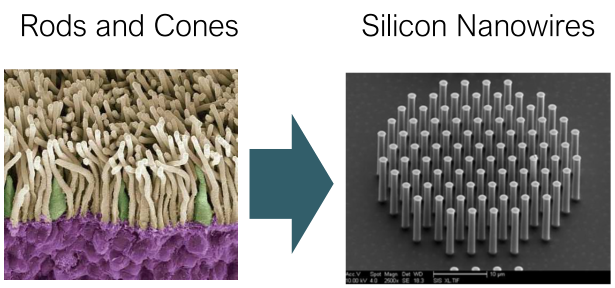
# Our Approach



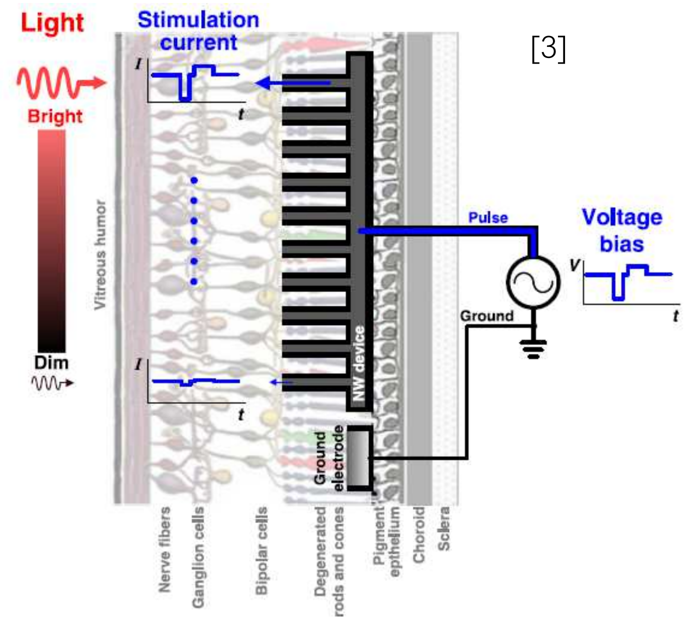
# A Scalable Subretinal Retinal Prosthesis

Nanovision has developed an optically-addressable silicon nanowire-based subretinal neurostimulator



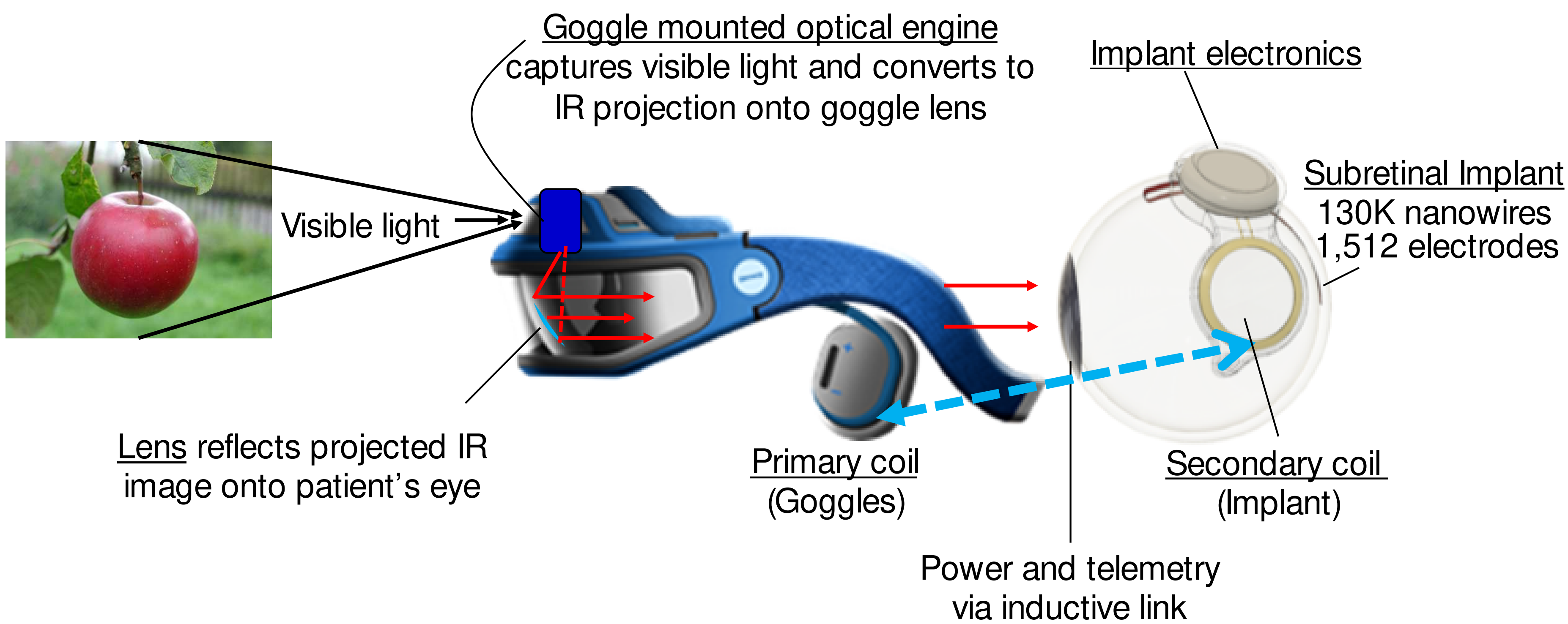

Degenerating photoreceptors are replaced with nanowire photosensors




Only 2 leads for biasing

[3] Ha, et al., Journ. Neuroeng., 2017.

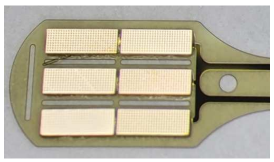
# Nanovision's Retinal Prosthesis System



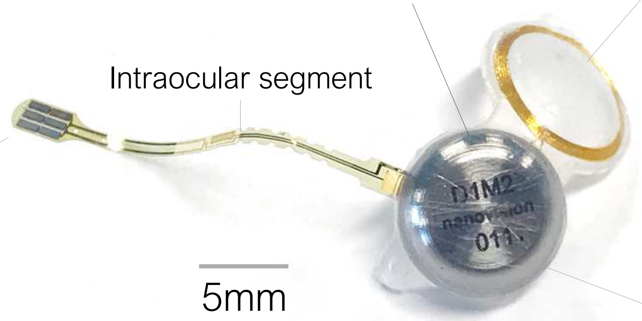
# Nanovision's Implantable Subretinal Prosthesis

nanovision

## Subretinal neurostimulator

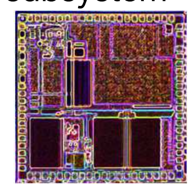


- >130,000 silicon nanowires
- 1,512 IrO pixels
- 50μm pitch, VA: 20/200
- Optically addressable array
- Multi-layer encapsulation




## 3D-coil antenna for wireless power & telemetry via an inductive link [1]

## Adiabatic electronics subsystem [2]



- Proprietary mixed-signal ASIC
- RF power harvesting
- Charge-balanced stimulation
- Adjustable pulse generation
- Telemetry

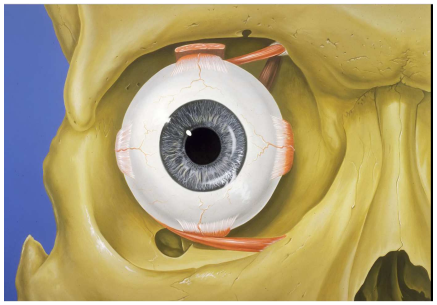
## Biocompatible Hermetic Package

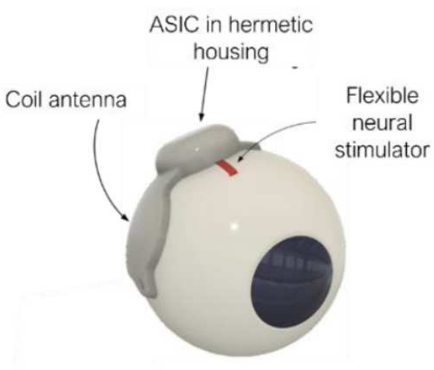
- Only 4 wired connections
- Robust metal-ceramic hermetic housing for electronic components
- Ultrathin intraocular neural stimulator optimized for surgical ease*

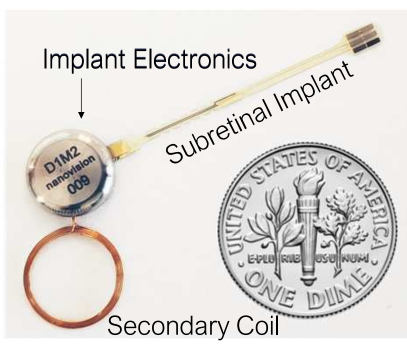
[4] Akinin, et al., IEEE EMBS NER, 2021. [5] Akinin, et al., IEEE ISSCC, 2021

# Package Mechanical Design Considerations

nanovision





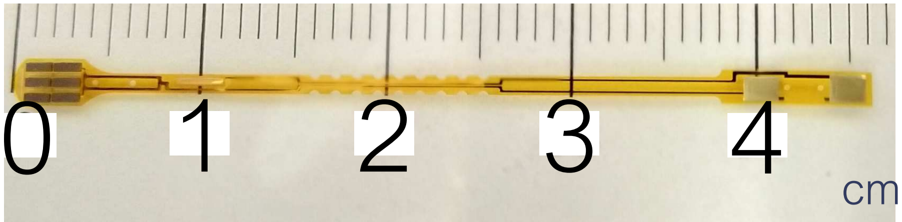

- The small size of the eye globe (<u>Ø≈24.1mm</u>) and presence of <u>6 ocular muscles</u> constrain mass and volume of extraocular components
- Intraocular electrode array attributes:
  - Flexibility
  - Ultrathin
  - Avoid sharp corners or edges
  - Size to minimize scleral incision
  - Allow sufficient perfusion

# Subretinal Neural Stimulator

**The subretinal neural stimulator employs an ultrathin chip-on-flex integrated platform** for smart, high resolution, distal neurostimulation

Innovations include:

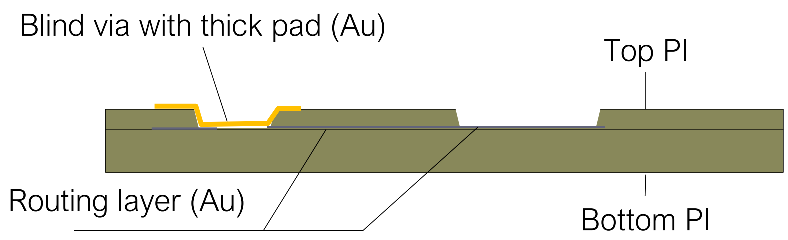
- Ultrathin flex circuit design
- Biocompatible materials
- Panel-level thin-film fabrication
- Thin die preparation
- Chip-on-flex bonding

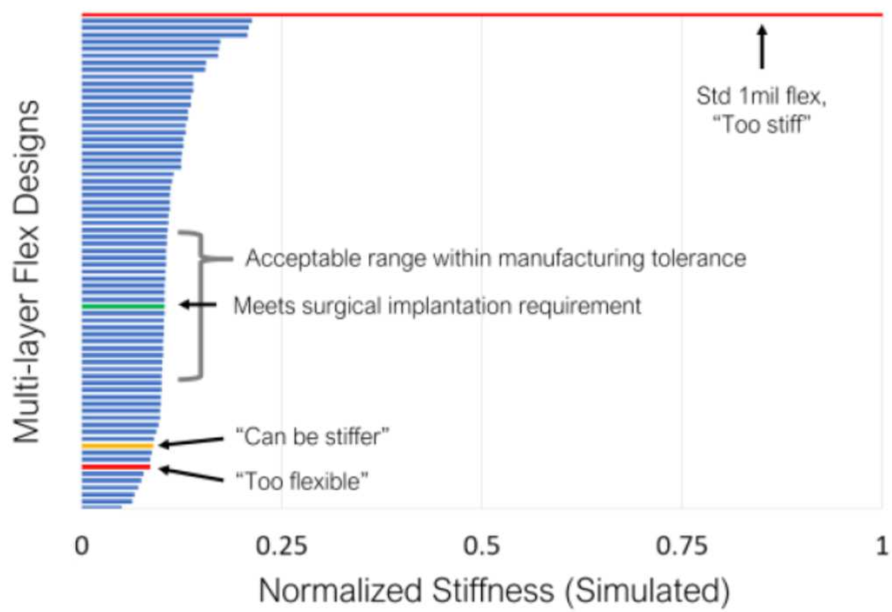


# Flex Circuit Design & Thin Film Fabrication

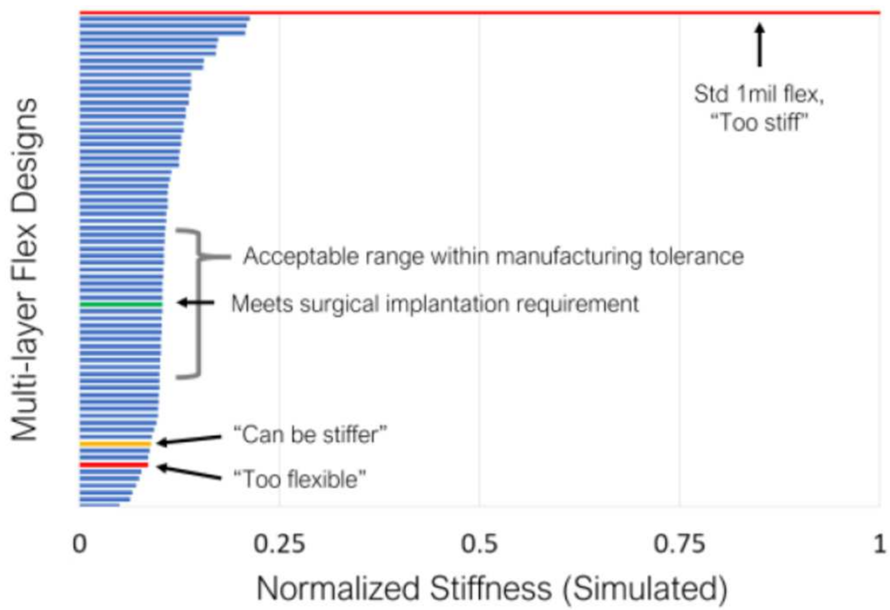
nanovision

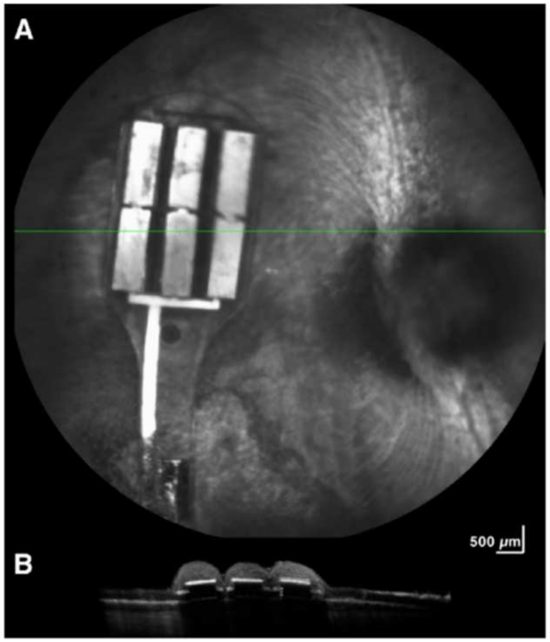
The ultrathin flexible circuit stack-up consists of two polyimide layers and two metal layers (1 internal + 1 external) for signal redistribution, dielet-attach and interconnection.



# Flex Circuit Design & Surgical Implantation

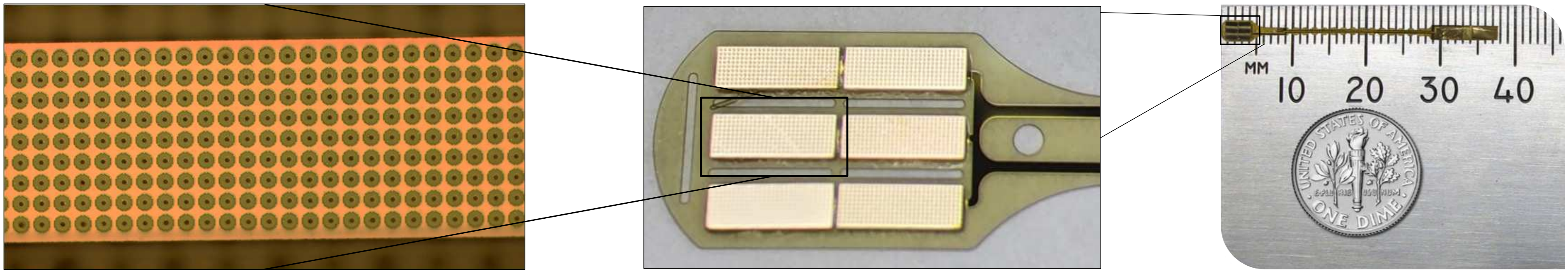


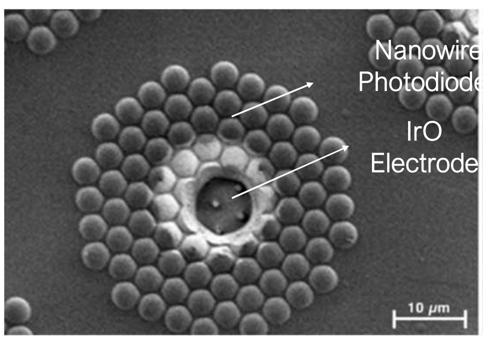






[6] Bosse, et al., Invest Ophthalmol Vis Sci. 2018 Dec; 59, 5885 [7] Xiao, et al., Invest Ophthalmol Vis Sci. 2018, 59, 4560

# Thin Die Preparation



Single pixel

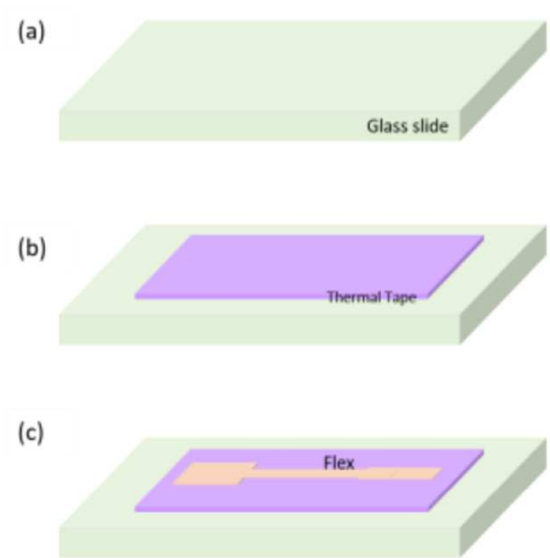
The intraocular stimulating electrode array comprises 6 silicon dielets

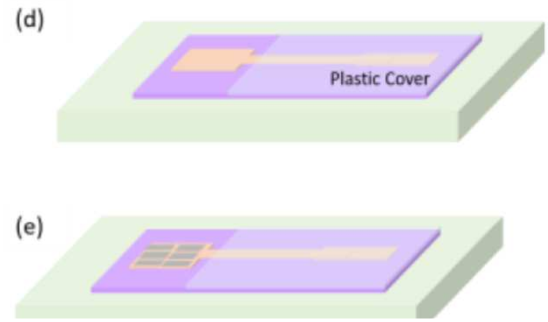
- Device has total 1512 electrodes (6 tiles x 252 pixels/tile)
- Fabricated using ***CMOS compatible processing***
- Thinned to <75um using ***standard grinding and polishing*** operations, finished with a ***backside contact***
- ***Diced*** to 1.4mm x 0.4mm
- ***Bonded*** to the ultrathin flex



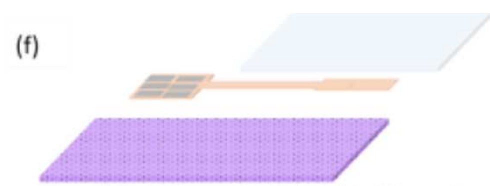
[8] Y. Jing, et al., IOVS, **58**(2017)

# Single Device Chip-on-Flex Bonding

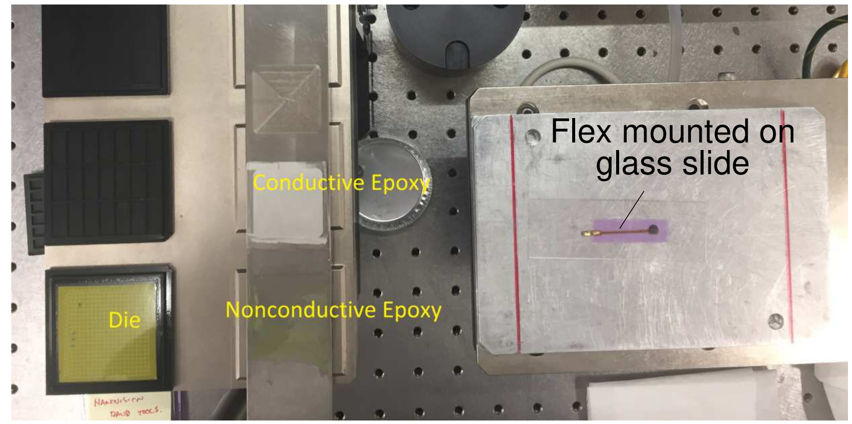


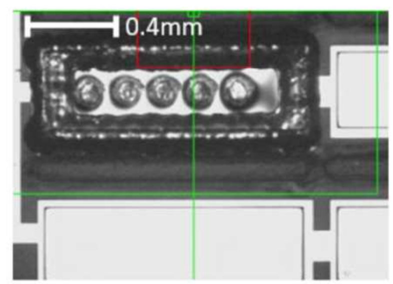

Bonded Flex: 120°C Oven Curing, 15 mins

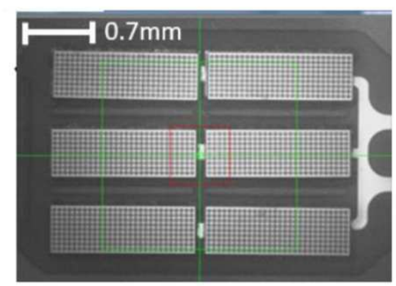



Thermal Tape Release:
180°C Hot Plate, 10 seconds



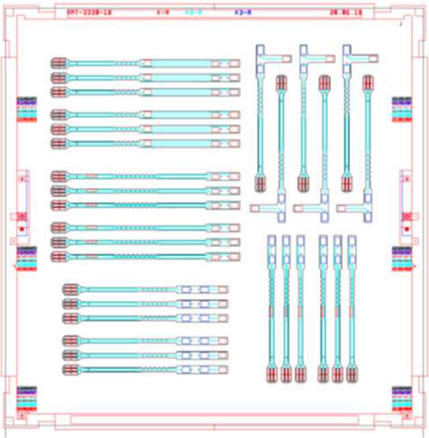

Epoxy Dispense Pattern

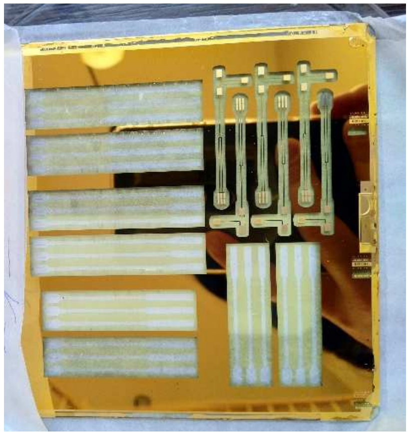


# Panel-Level Bonding

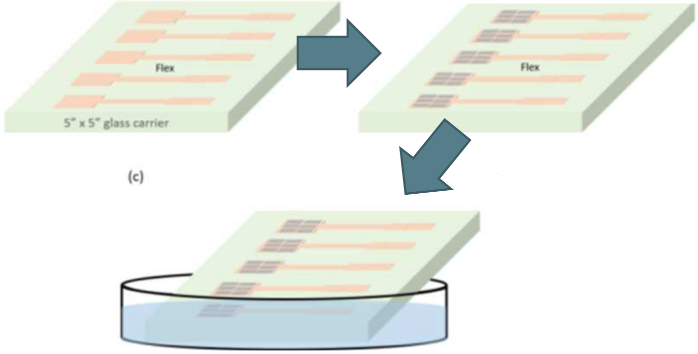
1. Arrays of ultrathin flex circuits are fabricated on a 5” x 5” glass carrier





2. The die bond locations can be accurately programmed from the CAD layout into the bonding equipment

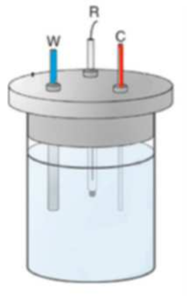
3. Multiple neural stimulators can be assembled via a die-to-panel process flow



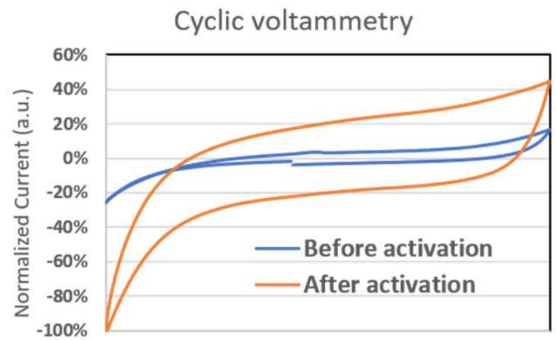

4. Once die to panel assembly is complete, multiple assembled flex circuits can be released in parallel

# Electrochemical Testing for Post-Bonding Verification

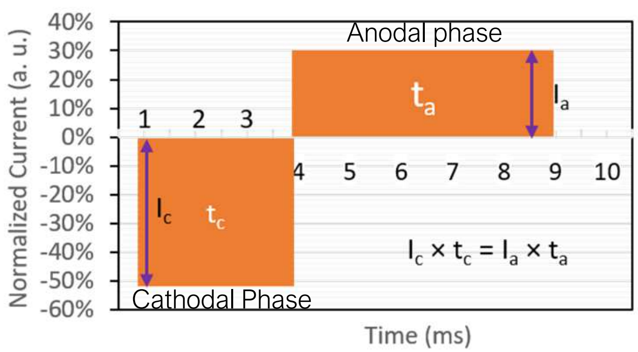
1. SIROF electrode activation by Cyclic Voltammetry

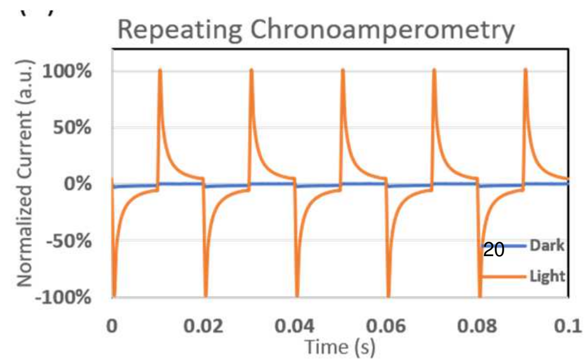



W: Working electrode, device under test.
R: Reference electrode: Ag/AgCl
C: Counter electrode: Pt wire.



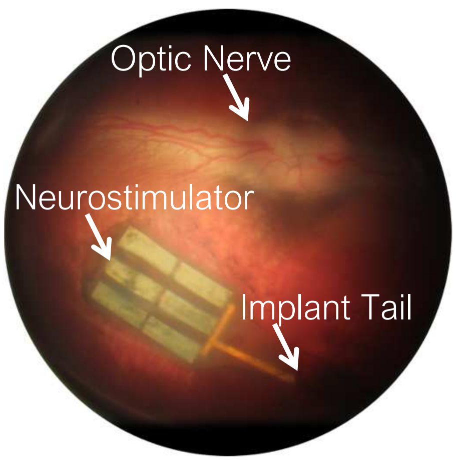

2. Assembly validation by repeating Chronoamperometry, where electrical stimulation is applied as a series of biphasic current pulses

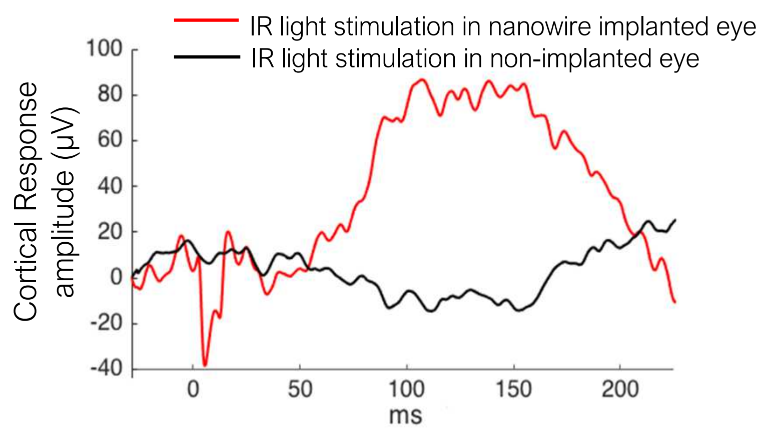


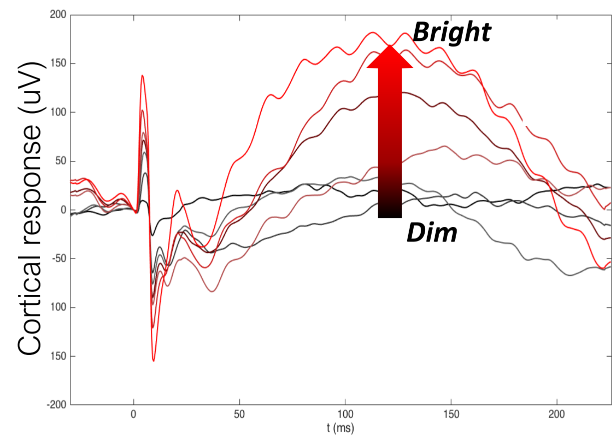
# Nanovision Implant Confirms Cortical Signals in Rabbits

nanovision




Stimulation of the nanowire prosthesis by IR light creates response in visual cortex

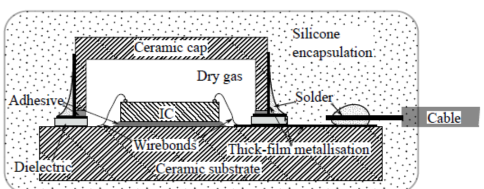



Cortical response signal gets stronger with brighter illumination

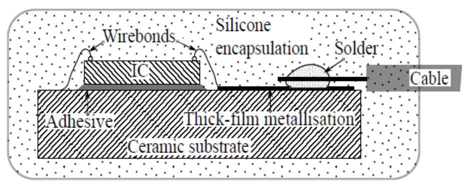
[1] Bosse, et al., Invest Ophthalmol Vis Sci. 2018 Dec; 59, 5885 [2] Xiao, et al., Invest Ophthalmol Vis Sci. 2018, 59, 4560

# Reliability for Implantable Stimulator

- Encapsulation is critical for a long-term implantable
- Hermetic encapsulation – robust, proven, can be bulky
- Non-hermetic encapsulation: smaller form factor, but not commercially mature
- Retinal prosthesis suited for a hybrid encapsulation approach → all electronics in hermetic housing; stimulator array uses non-hermetic encapsulation

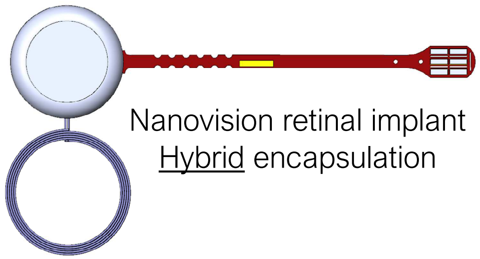



Hermetic




Non-hermetic

*Retinal Prosthesis* – Hybrid Encapsulation



Nanovision retinal implant
Hybrid encapsulation

# Biocompatible Materials for Neuron Implants

nanovision

**Table 1 | Summary of key materials used in the various device platforms of Figs. 1 and 2**

| Studies | Subject | Key materials | Thickness (μm) | Bending stiffness ($Nm^2$) | Functions | Operational lifetime in vivo[a] |
|---|---|---|---|---|---|---|
| Ref. [29] | Rat | Polyimide/gold | 4–6 | – | Recording/stimulation | – |
| Ref. [30] | Rat | Parylene/CNT | 3.5 | $3.3 \times 10^{-12}$ | Recording/stimulation | 10 weeks |
| Ref. [31] | Mouse | Epoxy/platinum | 0.9 | $1.4 \times 10^{-16}$ | Recording | 3 months |
| Ref. [34] | Rodent | Parylene/PEDOT:PSS | 4 | – | Recording | 10 days |
| Ref. [35] | Rat | Parylene/PEDOT:PSS | 2.6 | – | Recording | – |
| Ref. [37] | Rabbit | Polyimide/gold/SMP | ~100 | $1.0 \times 10^{-10}$ | Recording/stimulation | – |
| Ref. [39] | Feline | Polyimide/gold | 2.5 | – | Recording | 4 weeks |
| Ref. [40] | Rodent | Epoxy/platinum | 1 | $8.7 \times 10^{-11}$ | Recording | – |
| Ref. [41] | Rat | Polyimide/gold | 7 | – | Recording/stimulation | – |
| Ref. [45] | Rat | Parylene/PEDOT:PSS | 4 | – | Recording | – |
| Ref. [47] | Rat | $SiO_2$/titanium nitride | 20 | – | Recording | 153 days |
| Ref. [49] | Rat | Epoxy/Si-NW | 1 | $6.2 \times 10^{-12}$ | Recording/stimulation | – |
| Ref. [50] | Rat | Epoxy/Si-NW | 1 | $0.64 \times 10^{-15}$ | Recording/stimulation | – |
| Ref. [52] | Rat | Epoxy/Si-NM | ~20 | – | Recording | – |
| Ref. [53] | Rat | LCP/Si-NM | 50 | – | RFID | 6 weeks |

Constituent materials involve CNTs, SMPs, Si-NWs and Si-NMs, with system functions that include recording, stimulation and radio-frequency identification (RFID). [a]Operational lifetimes in vivo refer to the experimental timescales demonstrated in animal models in each case.

Song, Enming et al. "Materials for flexible bioelectronic systems as chronic neural interfaces." Nature Materials 19 (2020): 590-603.

# Accelerated Lifetime Testing

- Accelerated Aging calculation is based on Arrhenius' equation - a 10°C increase in temperature doubles the rate of chemical reaction.

The study duration is determined by the temperature the devices will be tested for accelerated aging(TAA) and the normal operating temperature (TRT).

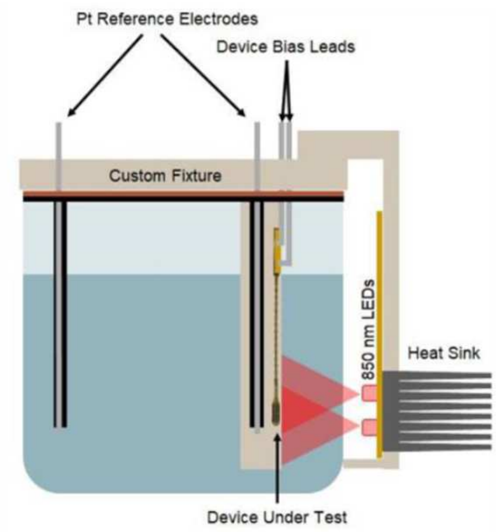
Accelerated Aging Factor (AFF)1 Day at TAA$^{o}$C = Q10((TAA –TRT)/10)Days at TRT$^{o}$C

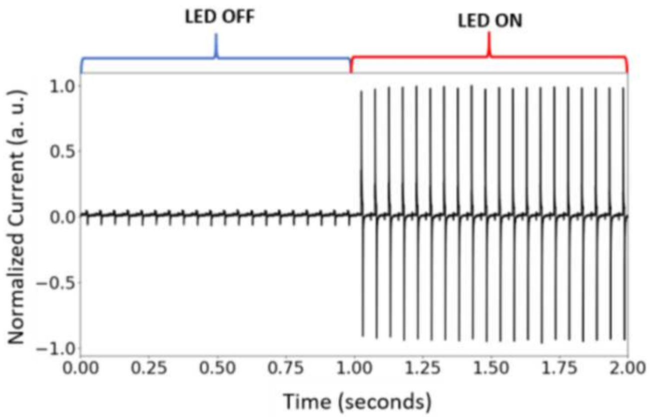
For a TAA of 60oC Accelerated aging factor = 2((60 –37)/10) = 22.3 = 4.92Test duration for 5-year equivalency = 1826.25 days / 4.92 = 371 days

- Light source: 850nm LEDs, monitored by commercial photosensors.
- Incubator temperature: 60°C
- Device Bias: 1.5V/ - 0.5V, Biphasic Waveform
- Device under Test (DUT) soaked in Dulbecco's phosphate-buffered saline solution to mimic harsh environment in the eye

# Accelerated Lifetime Testing

- Mechanical Fixture:
  - Non-reactive materials
  - Position-secured for DUT, and reference Ag/AgCl, Pt electrode
  - Bias Leads for DUT
  - Positioning the light source



# Summary

- The stimulator arrays that interface with delicate retina tissue are a critical component of retinal implants.
- The neural stimulator in Nanovision's retinal prosthesis is formed with a flexible substrate and silicon dielets.
- We described the design and development of the flexible circuits based on mechanical finite element analysis and feedback from the surgical team.
- The assembly process between the silicon dielets and the flex was also presented, followed by the electrochemical testing, and the approach to accelerated lifetime testing.
- The architecture described in this paper can be applied to future higher density retinal prosthetic array.
- The characterization techniques presented can be applied to different neural stimulation arrays.

nanovision

# Thank you

Questions?

yuhsin@nanovisionbio.com

Yu-Hsin Liu, Yi Jing, Brandon Bosse, Samir Damle,
Abraham Akinin, Sue Bauchner, Hiren D. Thacker