The Eye and The Chip
World Congress on Artificial Vision

12th WORLD RESEARCH CONGRESS

on the Relationship between Neurobiology and Nano-Electronics Focusing on Artificial Vision

October 3-5, 2021
Virtual Event
Detroit, Michigan

Henry Ford Health System

DEPARTMENT OF OPHTHALMOLOGY

Detroit Institute of Ophthalmology

2021 The Eye and The Chip World Research Congress

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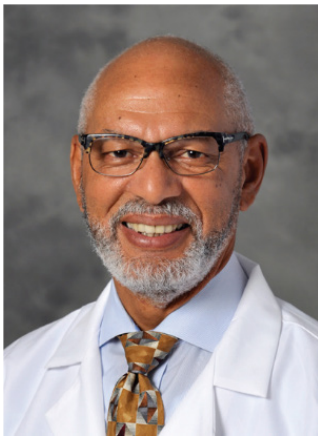

Welcome

On behalf of the Department of Ophthalmology, welcome to The Eye and the Chip 2021 World Research Congress. The World Congress planning team, have brought together the world's foremost experts on the development of neuro-prosthesis for vision restoration for patients who are blind or severely vision impaired. We are committed to having the Detroit Institute of Ophthalmology continue in its role of coordinating research on neuro-prosthetic devices and the physiology of retinal ganglion cell and cortical stimulation to augment the quality of vision from these devices and to continue to present our work for discussion to move the science forward.

As a clinician, I look forward with anticipation to the day when we can offer our patients technologies that are significantly more advanced, allowing them more natural vision.

Thank you to the entire organizing committee for their hard work in helping to plan the Congress. I would like to also take this opportunity to thank our esteemed panel of presenters who have outstanding research data to present. Finally, I would also like to thank each of our attendees for participating in this year's Congress. I am delighted that you are joining us and hope that you find the presentations and conversations very valuable and informative.

Sincerely,

Paul A. Edwards, M.D., F.A.C.S.
Chairman
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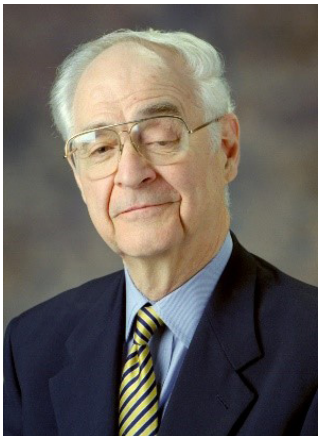
Department of Ophthalmology
Henry Ford Health System



We welcome you to **The Eye and The Chip 2021**, our 12th World Congress on the relationship between neurobiology and nano-electronics focusing on artificial vision.

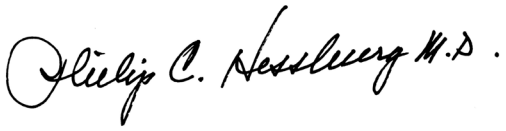
In 1998, as the Board of Directors of the Detroit Institute of Ophthalmology considered the research congress model first established in ophthalmology by the Welsh Cataract Congresses at the dawning of the era of intra-ocular lenses, we sought a suitable subject. After much deliberation visual neuro-prosthetics seemed just right.

At its emergence, around the world there were a group of scientists who thought the dream of visual nano-electronic prosthetic vision worth pursuing. Among the leaders of this initiative from the United States: Alan Chow in Chicago, Dick Normann in Salt Lake City, Joseph Rizzo in Boston, (co-organizer of these congresses since their inception), Robert Greenberg in California, Phil Troyk in Chicago, Greg Auner in Detroit, Gislin Dagnelie in Baltimore, Eugene deJuan in Los Angeles; from Germany Rolf Eckmiller in Bonn, Eberhart Zrenner in Tuebingen, Heinrich Gerding in Munster; and the Australians Greg Suaning and Nigel Lovell, along with Japan's Tohru Yagi, and Korea's Hum Chung. Some of these early investigators remain active to this very day and will be with us for The Eye and the Chip 2021.

As each biennial "Chip" congress has unfolded here in Detroit we have come closer to implants truly capable of satisfying our blind patients. We still have a distance to go but we now know in this Covid-ized world that despite discouragements, setbacks, viral pandemics, disappointments, and heartbreaks —- our dreams, our hopes, our goals are still very much alive.

God willing, those who have been loyal to this effort will one day conquer the challenges of the neural coding of the retina – of the brain – and will so elegantly improve our devices that one day we truly will lift a portion of the burden of those who suffer loss of sight.

These early pioneer scientists are nothing if not resolute and courageous in their efforts. Let us all celebrate the devotion, the integrity, the courage of these pioneers. Many of them have been loyal to this dream for large chunks of their academic lives and are with us this year, a full two decades later. They deserve our applause!



Philip C. Hessburg, M.D.
Medical Director, Detroit Institute of Ophthalmology
Senior Staff Ophthalmologist, Henry Ford Health System

The DIO: Support for the Visually Impaired, Education and Vision Research

Imagine having very poor vision or not being able to see at all. Now imagine an organization that helps you and your family – and one that's a world leader in bringing together researchers studying advances in eyesight and vision.

Since 1972 that's been the mission of the Detroit Institute of Ophthalmology. In 2012 the DIO joined the Henry Ford Health System serving as the research and education arm of the HFHS Department of Ophthalmology. The DIO exists to assist and educate the visually impaired helping them maintain independence and dignity and live satisfying lives in a sighted world. The DIO also sponsors international research congresses that annually bring together the world's leading vision-related scientists.

To help the blind and visually impaired maintain the highest quality of life, the DIO offers a comprehensive range of support services. These include:

Support Groups

For more than four decades, the DIO has sought to help those who suffer from vision loss by managing support groups for the visually impaired. These groups are offered at various locations in southeast Michigan. All groups offer hope, joy, compassion, understanding and interaction with others who are similarly challenged. Thanks to Edward T. and Ellen K. Dryer Charitable Foundation and The Mary Thompson Foundation for their support.

Martha F. Gorey Resource Center

Named for a long-time benefactor and housed within the DIO, the Center offers one of the largest collections of low-vision aids in southeast Michigan. These include closed-circuit magnifying machines, hand-held and stand magnifiers up to 3x, large-print calendars, talking watches, clocks and calculators.

Education

The DIO provides a variety of educational resources to both the visually-impaired and sighted communities, including:

- **Professional Education:** DIO is closely affiliated with the ophthalmic technician training program at Henry Ford College, Dearborn, and the Henry Ford Health System Department of Ophthalmology's Residency Training program. One of the physicians of the DIO serves as both the Medical Director for the Henry Ford College Ophthalmic Technician Training Program and as the Residency Program Director and Vice Chair of Education for the Department of Ophthalmology at Henry Ford Hospital. Throughout the year, various workshops for training physicians in internal medicine and emergency medicine are conducted at the DIO.
- **Public Education:** DIO participates at Assumption Senior Expo providing information and resources for visually impaired seniors and their families.

Research Congresses

The DIO sponsors two international vision-related research congresses that assemble more than 30 of the world's top vision-related scientists for three days of meetings and seminars in Detroit. Alternating each year, these congresses are: The Eye, The Brain and The Auto, and The Eye and The Chip. Find more information at: www.henryford.com/theeyeandthechip

Friends of Vision

Many DIO programs rely on support from its volunteer arm, the Friends of Vision. They provide support to the visually impaired in several ways, including helping to set up and provide transportation to meetings and events; escorting them on field trips; staffing the Martha F. Gorey Resource Center store; and participating in such events as managing the cash raffle at the EyesOn Design Car Show. Volunteers receive necessary training and choose the activities that best match their schedules and interests.

DIO Support

In addition to the EyesOn Design events, DIO programs are supported by generous donations from individuals, foundations and corporations. The many ways you can help include:

- Bequests
- Fundraisers / special events
- Donations of time and/or money
- Honorary / memorial gifts
- Endowments
- Matching funds

Through the commitment of a very generous donor, DIO has established the Philip C. Hessburg, M.D. Detroit Institute of Ophthalmology Endowed Lectureship: Progress in the Eradication of Blindness. Its purpose is to honor Dr. Hessburg and to ensure that the vital work of the Detroit Institute of Ophthalmology endures.

For more information, please call the DIO at (313) 824-4710 or visit henryford.com/DIO.

Henry Ford Health System Department of Ophthalmology

Board-certified physicians, with leaders in comprehensive ophthalmology and ophthalmic sub-specialties, including surgical care. Advanced treatment options led by continuous research. One of the largest practices in the United States, providing convenient, high-quality and compassionate care for over 75 years.

A leader in Michigan, as well as one of the largest ophthalmology practices in the United States, the Henry Ford Department of Ophthalmology treats more than 55,000 patients per year at 12 locations throughout Southeast Michigan.

Our ophthalmologists also work closely with Henry Ford Medical Group physicians in other departments, providing multidisciplinary, coordinated care for those patients who need it.

In addition, we are dedicated to vision research, helping to increase our understanding of disease processes and the most effective ways to detect, diagnose, treat and prevent these conditions. Ultimately, our extensive research program helps to break new ground in critical areas of vision research, keeping us at the forefront of innovation while advancing the level of eye care that we provide to our patients.

PROGRAM SCHEDULE

Sunday, October 3, 2021

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)
All times are Eastern Standard Times

7:55 – 7:58 a.m. **Welcome & Introduction**
Paul Edwards, M.D., Chair, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

7:58 – 8:00 a.m. **Housekeeping Announcements**
David Goldman, M.D., M.B.A, Residency Director, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session One: Retinal Prosthetics Studies
Moderator – Gregg Suaning, Ph.D., University of Sydney, Australia

8:00 - 8:30 a.m. Simulating the Effects of Persistence and Perceptual Fading in Retinal Prosthetic Vision
David Avraham, M.Sc., Schepens Eye Research Institute, Boston, Massachusetts

8:30 - 9:00 a.m. Effects of Different Subretinal Implant Designs on the Retina in Mini-pigs and Drug Induced Incomplete Outer Retinal Degeneration in Cynomolgus Monkey
Seong-Woo Kim, Ph.D., Korea Consortium for Retinal Prosthesis Development, Seoul, Korea

9:00 - 9:30 a.m. FDA Device Update
Michelle Sandrian, Ph.D., F.D.A, Silver Spring, Maryland
Elvin Ng, Assistant Director for Retinal and Diagnostic Team, F.D.A., Silver Spring, Maryland

9:30 – 9:45 a.m. **BREAK**

Session Two: Clinical Reports- Cortical
Moderator – Daniel Palanker, Ph.D., Stanford University, Stanford, California

9:45 - 10:15 a.m. Orion Visual Prosthesis System: Long-Term Clinical Trial Results
Jessy Dorn, Ph.D., Second Sight Medical Products, Sylmar, California

10:15 – 10:45 a.m. Visual Percepts Evoked with an Intracortical 96-Channel Microelectrode Array Inserted in Human Visual Cortex
Eduardo Fernandez, M.D., Ph.D., University of Miguel Hernandez, Elche, Spain

10:45 - 11:15 a.m. Intracortical Visual Prothesis (ICVP): First Phase of the Clinical Trial
Philip Troyk, Ph.D., Illinois Institute of Technology, Chicago, Illinois

11:15 - 12:15 p.m. **GROUP DISCUSSION**
Moderators: Daniel Palanker and Gregg Suaning

12:15 - 1:15 p.m. **LUNCH**

Session Three: Clinical Reports - Retina
Moderator- Shelley Fried, Ph.D., Harvard Medical School, Boston, Massachusetts

1:15 – 1:45 p.m. Long Term Visual Results of Prima Chip in Patients with Geographic Atrophy
Yannick Le Mer, M.D., Foundation Ophthalmology A. de Rothschild, Paris, France

1:45 - 2:15 p.m. Effects of Intra-orbital Mechanical Forces on Subretinal Implant ALPHA: Displacements of Subretinal Chips and Assessment of Cable Movement by Dynamic Computer Tomography during Gaze Changes
Eberhart Zrenner, M.D., Ph.D., University of Tübingen, Tübingen, Germany

2:15 – 2:30 p.m. **BREAK**

Session Four: Psychophysics
Moderator: James Weiland, Ph.D., University of Michigan, Ann Arbor, Michigan

2:30 - 3:00 p.m. Variability in Relative Phosphene Mapping Techniques: Fine Tuning Local Clusters
Liancheng Yang, M.Sc., Johns Hopkins University, Baltimore, Maryland

3:00 – 3:30 p.m. Assessing Visual Acuity in Low and Ultra Low Vision Using Steady-State Visual Evoked Potentials
Leili Soo, Ph.D., CORTIVIS, Elche, Spain

3:30 - 4:00 p.m. Shape Perception via High-channel-count Neuroprosthesis in Monkey Visual Cortex
Xing Chen, M.Sc., Netherlands Institute for Neuroscience, Amsterdam

4:00 – 5:00 p.m. **GROUP DISCUSSION**
Moderators: Shelley Fried and James Weiland

5:00 – 5:15 p.m. **BARTIMAEUS AWARD CEREMONY**

5:15 – 6:00 p.m. **UNSTRUCTURED NETWORKING**

Monday: October 4, 2021

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)
All times are Eastern Standard Times

7:55 – 7:58 a.m. **Welcome & Introduction**
Paul Edwards, M.D., Chair, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

7:58 – 8:00 a.m. **Housekeeping Announcements**
David Goldman, M.D., M.B.A, Residency Director, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session Five: Retinal Stimulation Strategies
Moderator: Eduardo Fernandez, M.D., Ph.D., University Miguel Hernandez, Elche, Spain

8:00 - 8:30 a.m. Characterizing Electrical Response Properties of Retinal Ganglion Cells using Gaussian Noise Stimulus
Hamed Shabani, M.S., Tübingen Retinal Implant Group, Tübingen, Germany

8:30 - 9:00 a.m. Morphological Features of RGC's and Their Influence on Threshold to Electric Stimulation
Paul Werginz, Ph.D., Massachusetts General Hospital and Vienna, Austria

9:00 - 9:30 a.m. Mechanisms Underlying Differential RGC Responses to Low vs. high Rate Stimulation
Jae-Ik Lee, Ph.D., Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

9:30 – 9:45 a.m. **BREAK**

Session Six: Retinal Stimulation Strategies
Moderator: Eberhart Zrenner, M.D., Ph.D., University of Tübingen, Tübingen, Germany

9:45 - 10:15 a.m. Electronic "Photoreceptors" Enable Prosthetic Vision with Acuity Matching the Natural Resolution in Rats
Daniel Palanker, Ph.D., Stanford University, Stanford, California

10:15 - 10:45 a.m. Toward High-acuity Prosthetic Vision Based on Optically Configurable Confinement of Electrical Field with Photovoltaic Pixels
Charles Chen, M.Sc., Stanford University, Stanford, California

10:45 – 11:15 a.m. **GROUP DISCUSSION**
Moderator: Eduardo Fernandez and Eberhart Zrenner

11:15 - 12:00 p.m. **LUNCH**

Session Seven: Utilizing Virtual Reality and Artificial Intelligence
Moderator: Daniel Rathbun, Ph.D. Henry Ford Health System, Detroit, Michigan

12:00 - 12:30 p.m. Immersive Virtual Reality Simulations of Bionic Vision
Justin Kasowski, B.Sc., Bionic Vision Lab, Santa Barbara, California

12:30 - 1:00 p.m. Hand-Eye Coordination in Virtual Reality Under Simulated Prosthetic Vision Conditions
Gislin Dagnelie, Ph.D., Johns Hopkins University, Baltimore, Maryland

1:00 - 1:30 p.m. Towards a Smart Bionic Eye: The Emerging Role of Computer Vision and AI for Artificial Vision
Michael Beyeler, Ph.D., Bionic Vision Lab at University California, Santa Barbara, California

1:30 - 3:30 p.m. **UNSTRUCTURED NETWORKING**

Session Eight: The Aussie Special
Moderator: Gislin Dagnelie, Ph.D., Johns Hopkins University, Baltimore, Maryland

3:30 - 4:00 p.m. Vision Processing Methods to Facilitate Functional Vision in Participants Implanted with a Suprachoroidal Retinal Prosthesis: The Evidence to Date for Conditions with Poor Contrast
Nick Barnes, Ph.D., The Royal Victorian Eye & Ear Hospital, Melbourne, Australia

4:00 - 4:30 p.m. Controlling Neuronal Activity of Retinal Ganglion Cells Using Dynamic Frequency Modulation
Madhuvanthi Muralidharan, M.E., University of New South Wales, Sydney, Australia

4:30 - 5:00 p.m. Methods for Neural Activity Shaping in the Presence of Electrode Crosstalk
Martin Spencer, Ph.D., Bionic Vision Technologies, Melbourne, Australia

5:00 - 5:45 p.m. **GROUP DISCUSSION**
Moderators: Daniel Rathbun and Gislin Dagnelie

5:45 - 6:00 p.m. **BREAK**

6:00 - 9:00 p.m. **POSTER SESSION – More information to follow**

Tuesday, October 5, 2021

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)
All times are Eastern Standard Times

7:55 – 7:58 a.m. **Welcome & Introduction**
Paul Edwards, M.D., Chair, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

7:58 – 8:00 a.m. **Housekeeping Announcements**
David Goldman, M.D., M.B.A, Residency Director, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session Nine: New Materials
Moderator: Greg Auner, Ph.D. Wayne State University, Detroit, Michigan

8:00 - 8:30 a.m. Microfabrication and Biocompatibility of Subretinal Electrode Arrays
Doug Shire, Ph.D., Bionic Eye Technologies, Ithaca, New York
Joseph Rizzo, M.D., Harvard Medical School, Boston, Massachusetts

8:30 - 9:00 a.m. Soft Organic Neural Interface for Recording and Stimulating the Intact Retina
Ieva Vebraite, M.Sc., Tel Aviv University, Tel Aviv, Israel

9:00 - 9:30 a.m. Light-Intensity-Controlled Stimulation of Neurons by an Organic Photovoltaic Interface
Shashi Srivastava, Ph.D., Koc University, Istanbul, Turkey

9:30 – 9:45 a.m. **BREAK**

Session Ten: Cortical Stimulation and Use of Eye Tracking
Moderator: Joseph Rizzo, M.D., Massachusetts Eye and Ear Infirmary - Harvard Medical School, Boston, Massachusetts

9:45 -10:15 a.m. Utility of Eye Tracking in Visual Cortical Prostheses - Preliminary Patient Testing Results
Avi Caspi, Ph.D., Second Sight Medical Products, Jerusalem, Israel

10:15 – 10:45 a.m. Development of a Closed-loop Approach for Automatically Adjusting Thresholds in Cortical Visual Prostheses
Fabrizio Grani, M.Sc., CORTIVIS, Spain

10:45 - 11:15 a.m. Responses of Visual Cortical Neurons to Aperiodic Electrical Stimulation of the Retina
Zixen Ye, B. Sc., City University of Hong Kong, Hong Kong, China

11:15 – 11:45 a.m. **BREAK**

Session Eleven: Cortical Alternatives to Electrical Stimulation
Moderator: Philip Troyk, Ph.D., Illinois Institute of Technology, Chicago, Illinois

11:45 – 12:15 p.m. Towards the Development of a Micro-coil Based Cortical Visual Prosthesis
Shelley Fried, Ph.D., Harvard Medical School, Boston Massachusetts

12:15 – 12:45 p.m. Micro-magnetic Stimulation of Primary Visual Cortex (VI) Elicits Focal Activation of Secondary Visual Cortex (V2)
Seung Woo Lee, Ph.D., Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

12:45 - 1:15 p.m. Photochemical Damage Implications to Optogenetic Forms of Cortical Prosthesis
John Exton, M.Sc., Newcastle University, Newcastle, United Kingdom

1:15 – 2:15 p.m. **GROUP DISCUSSION**
Moderators: Greg Auner, Joseph Rizzo, and Philip Troyk

2:15 – 2:45 p.m. **WRAP-UP DISCUSSION – END OF MEETING**
Moderators: Philip Hessburg and Joseph Rizzo

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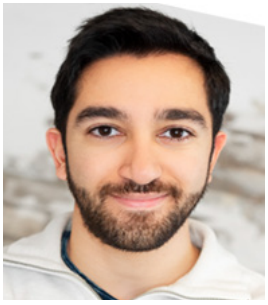
2021 World Congress:
The Eye and The Chip

SPEAKER ABSTRACTS

Photo from the 2019 The Eye and The Chip



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Simulating the Effects of Persistence and Perceptual Fading in Retinal Prosthetic Vision

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Purpose: Simulating temporal aspects, such as persistence and perceptual fading of phosphenes, in retinal prosthetic vision may shed light on the complex visual experience of implanted patients, improve their training, and help defining the temporal parameters of new prosthetic devices.

Methods: We built a prosthetic simulation tool. An input video is converted to grayscale and divided into frames. Each frame is divided into blocks according to the number of simulated electrodes chosen by the user. The angular field of view spanned by the electrode array is also set by the user. The temporal model is being integrated into each frame and a simulated prosthetic video is displayed. The temporal model includes: 'persistence', which relates to the perception of a phosphene following stimulation offset, 'perceptual fading onset', which is the moment at which phosphenes begin to fade during a continuous stimulation due to a desensitization of retinal ganglion cells (RGCs), and 'perceptual fading period', which is the period in which phosphenes disappear following the perceptual fading onset.

Results: Persistence of phosphenes may add an artifact; bright objects may become smeared (see Figure 1(a)) while dark objects are sometimes masked by the persistence of the bright background. Perceptual fading of phosphenes may cause static objects to completely disappear (see Figure 1(b)) and dynamic objects to partially disappear. The disappearance may be counteracted by head movements. We show the benefit of this effect.

Biography: David Avraham received his M.Sc. degree in Electro-Optical Engineering from Ben Gurion University, Israel, in 2018. He is currently pursuing his Ph.D. degree in the same department. Since 2017 he is also a Research Fellow with the Schepens Eye Research Institute, Harvard Medical School, Boston, MA. His research interests include prosthetic vision, computer vision, and 3-D imaging.

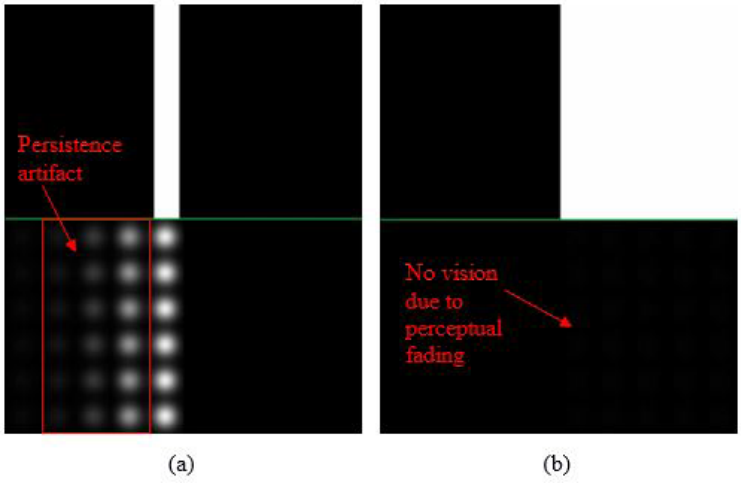

Figure 1: Video frames showing the effects of persistence and perceptual fading. (a) A dynamic stimulus is smeared due to a persistence period of 4 seconds (video link). (b) A static stimulus fades at persistence period of 4 seconds, perceptual fading onset of 1 second, and perceptual fading period of 2 seconds (video link). The top segments represent a stimulus and the low segments represent prosthetic vision. The images represent a single frame of a video.

Conclusions. Persistence and perceptual fading of phosphenes play a large role on the perception of implanted patients and should be considered in training and future development of retinal prostheses.

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Vision Processing Methods to Facilitate Functional Vision in Participants Implanted with a Suprachoroidal Retinal Prosthesis: The Evidence to Date for Conditions with Poor Contrast

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Purpose: Research is limited for vision processing (VP) algorithms for prosthetic vision in implanted-participant trials, despite promising evidence that they can improve functional vision. We have developed and evaluated novel VP algorithms for the Bionic Vision Technologies suprachoroidal retinal prosthesis (BVT Gen2–NCT03406416) for end-stage retinitis pigmentosa (RP). This summary shows our VP algorithms could improve functional vision for tasks related to everyday activities, and in complex environments.

Method: Randomized controlled trials investigated the effectiveness of two novel VP algorithms for two functional vision tasks. (1) object detection and avoidance for effective orientation and mobility (O&M; Local Background Enclosure VP; LBE). Camouflaged white objects (small–large ground-based and overhanging, e.g., mannequin, chair, box; Fig. 1) were randomly placed in a white environment. (2) locating (verbal response) and reaching (final finger distance to object: cm) for common (e.g., cup, plate) tabletop objects (Detection of Color Contrast VP; DOCC). Red objects and the green tabletop have similar luminance; detection may be difficult without DOCC. Algorithm effectiveness was compared to System Off (SO) and state-of-the-art (i.e., Intensity; I) VP. Three participants with advanced RP (2 male, 1 female; 47–66 years) implanted unilaterally with the retinal prosthesis took part. Object type, position, and order of VP display were randomized. Data were pooled across participants for analyses.

Results: O&M: Object detection: LBE VP (M58.97±31.96%) had higher rates than I VP (M5.98±12.96%) and SO (M .00±.00%; P<0.0001). LBE VP had fewer collisions (M1.51±1.39) than SO (M2.53±2.15 P<0.05), and trending to fewer collisions than I VP (M2.46±2.09, P=.07 with medium Cohen's effect size=.54). Tabletop: localization: DOCC VP (59.42±49.46%) outperformed I VP (27.54±45.00%) and SO (P<.0001). DOCC VP (8.03±11.41cm) was associated with closer proximity than I VP (27.88±24.88cm) and SO (43.82±24.25cm; P<.0001).

Conclusion: For three individuals implanted with the BVT Gen2 retinal prosthesis, two novel VP methods show promise to enhance performance on functional vision tasks associated with every-day activities and independent living. The methods were robust to poor color contrast and consistently performed better than the state-of-the-art method.

Biography: Nick Barnes is a Professor at the School of Computing, at the Australian National University since 2021. He received a B.Sc. (Hons) in 1994 and Ph.D. in 1999 from the University of Melbourne. He was a visiting fellow at the University of Genoa, Italy in 1999. From 2000 to 2003 he was a tenured Lecturer at the University of Melbourne. He then joined NICTA in Computer Vision and became Research Group Leader in 2006. In 2011, he was appointed to the NICTA executive as a Research Group Leader, supervising more than 25 research staff. In 2012 he was promoted to Senior Principal Researcher at NICTA. From 2016 to 2019 he was a Senior Principal Researcher and the Research Leader for 3D Vision at Data61 (CSIRO), and an Associate Professor at the Australian National University.

His research interests are in Computer Vision, Computer Vision for Prosthetic Vision, and deep learning in computer vision, particularly for image segmentation, salient object detection, 3D vision and dense prediction. He has published more than 150 scientific publications on these topics. He was a Lead Investigator on the Bionic Vision Australia Special Research Initiative. His pioneering research in vision processing for prosthetic vision was a key contribution to the formation of Bionic Vision Technologies. This work was recognized the CSIRO Digital and National Facilities Science Excellence Award in 2017.

Fig 1: participant in the white O&M environment with white objects

Fig 2: participant reaches for a detected object

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Nick Barnes: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support); Data61, CSIRO (Patent) Janine Walker: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support)
Maria Kolic: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support)
Penelope Allen: Commercial Relationship(s); Centre for Eye Research Australia: (Patent); Bionic Vision Technologies Pty Ltd (Financial Support)
Matthew Petoe: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support); Bionics Institute (Patent) William Kentler: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support)
Jeremy Orloff: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support); Data61, CSIRO (Patent) Nariman Habili: Commercial Relationship(s); Bionic Vision Technologies Pty Ltd (Financial Support); Data61, CSIRO (Patent)

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Towards a *Smart Bionic Eye:* The Emerging Role of Computer Vision and AI for Artificial Vision

Introduction: A major outstanding challenge for the field of bionic vision is translating electrode stimulation into a code that the brain can understand. Rather than aiming to one day restore natural vision (which may remain elusive until we fully understand the neural code of vision), a Smart Bionic Eye would provide AI-powered visual augmentations to support scene understanding in specific real-world tasks that are known to diminish the quality of life of bionic eye recipients.

Methods: To guide the development of such a device, we developed a virtual reality (VR) prototype supported by simulated prosthetic vision (SPV) that lets users see "through the eyes of the patient" as they explore an immersive virtual environment. In this setup, the visual input about to be rendered to a head-mounted display mimicked the external camera of a retinal implant and was adjusted based on the user's head/eye movements and spatial location.

Importantly, we used an established and psychophysically validated computational model of bionic vision to generate realistic predictions of SPV, which can be fitted to a specific individual and their implant technology. As a proof of concept, we adopted several state-of-the-art computer vision algorithms to simplify the visual input to the simulated implant in real time (e.g., highlighting visually salient information, highlighting nearby obstacles, and segmenting objects of interest), and systematically evaluated the ability of these algorithms to support scene understanding in a range of orientation and mobility tasks.

Results: All tested scene simplification strategies improved behavioral performance compared to the encoding strategy commonly employed by current implant technologies (where pixel grayscale values are linearly mapped to stimulus amplitude). Object segmentation was identified as the most promising strategy to support outdoor scene understanding. However, perceptual performance was drastically affected by phosphene size and streak length, which highlights the importance of accounting for realistic phosphene shape when making predictions about prosthetic performance.

Conclusion: This work is a first step towards a Smart Bionic Eye. Our prototype has the potential to speed up the development process by allowing us to test theoretical predictions in high-throughput experiments, the best of which can then be validated in real bionic eye recipients.

Biography: Michael Beyeler directs the Bionic Vision Lab at UC Santa Barbara. He received a Ph.D. in Computer Science from UC Irvine as well as a B.S. in Electrical Engineering and a M.S. in Biomedical Engineering from ETH Zurich, Switzerland. Prior to joining UCSB, he completed a postdoctoral fellowship in the labs of Ione Fine (Psychology, Institute for Neuroengineering) and Ariel Rokem (eScience Institute) at the University of Washington, where he developed computational models of bionic vision. He is Associate Director of the UCSB Center for Virtual Environments and Behavior (ReCVEB) and recipient of the National Institutes of Health (NIH) K99/R00 Pathway to Independence Award.

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Utility of Eye Tracking in Visual Cortical Prostheses – Preliminary Patient Testing Results

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Restoring functional sight requires that the electrical stimulation should convey information to the brain that is associated with the correct spatial location in the scene. A visual cortex stimulator can bypass the eye and the optic nerve and create phosphenes (perception of light) without light entering the eyes. Nonetheless, recently we demonstrated that eye movements dominate the perceived location of cortical stimulation-evoked phosphenes, even after years of blindness. In the current presentation we will present results from patients demonstrating the correlations between eye movements and the visual percepts.

Eye movement can play several roles in a cortical visual prosthesis. Eye position dominates the perceived location of the percept. Additionally, by instructing patients to conduct an eye movement toward the phosphene, eye tracking can be used as a marker to construct the spatial map of the implanted cortical electrodes. Experiments were conducted with blind patients implanted with the NeuroPace Responsive Neurostimulator (RNS) and the Orion visual cortical prosthesis devices.

In a cortical visual prosthesis, the layout of the implanted array does not match a retinotopic map and it is therefore necessary to find the visual-field location of the percept of each implanted electrode. To establish the spatial map of the electrodes, users were instructed to conduct an eye movement to the location of the phosphene generated by electrical stimulation of the occipital lobe. Two different schemes were compared. In the first, a brief stimulation was presented, and the subject moved their eyes after the end of the stimulation toward the phosphene's remembered location. In the second, a longer stimulation was presented, and the subject moved their eye during the stimulation to track the phosphene's location. In the latter case because the stimulation is continuously mapped based on eye position, an eye movement during the stimulation caused the phosphene to move. Results show that subjects were able to conduct a smooth pursuit motion as a result of constant stimulation.

These experimental setups demonstrate that the integration of eye tracking recording can be used to create the spatial map of a cortical visual implant.

Biography: Dr. Caspi is a faculty member at the Department of Electrical and Electronics Engineering at Jerusalem College of Technology, previously, he worked and consulted to Second Sight Medical Product. He developed the fitting and image processing algorithms of the Argus II retinal prosthesis device. Dr. Caspi's research interests include eye movements and sensor integration for visual prosthesis devices.

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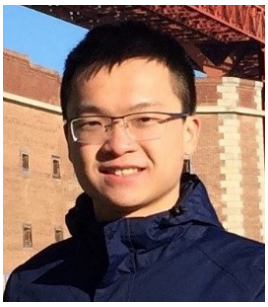
Shape Perception via a High-channel-count Neuroprosthesis in Monkey Visual Cortex

Blindness affects 40 million people worldwide, and a neuroprosthesis may restore functional vision in the future. We implanted a 1024-channel prosthesis in the monkey visual cortex and used electrical stimulation to elicit percepts of dots of light ('phosphenes') on hundreds of electrodes. Phosphene locations matched the receptive fields of the stimulated neurons, and V4 activity predicted phosphene detection during stimulation in V1. Next, we stimulated multiple electrodes simultaneously to generate percepts composed of multiple phosphenes. The monkeys could immediately recognize simple phosphene shapes, motions, or letters, demonstrating the potential of electrical stimulation to restore functional, life-enhancing vision in the blind.

Biography: Xing Chen is Senior Researcher and co-PI at the Netherlands Institute for Neuroscience, specializing in brain-computer interfaces, visual neuroscience, and blindness.

She uses innovative 3D modelling and printing techniques to create customized cranial implants for improved implant stability and animal welfare. She develops high-channel-count neuroprosthesis systems (1024 channels) for chronic recording and electrical stimulation of primate visual cortex, yielding demonstrations of the feasibility of artificial vision in the blind. Her work has been featured in both international and national newspapers and magazines, such as CNN, Science Magazine, Scientific American, NOS, NPO Radio, and RTL Nieuws.



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Toward High-acuity Prosthetic Vision Based on Optically Configurable Confinement of Electric Field with Photovoltaic Pixels

Zhijie Charles Chen1, Bing-Yi Wang2, Mohajeet B. Bhuckory3, Tiffany Huang1, Andrew Shin4, Ludwig Galambos5, Valentina Zuckerman5, Elton Ho2, Keith Mathieson6, Theodore Kamins1, and Daniel V. Palanker3,5
1Electrical Engineering, 2Physics, 3Ophthalmology, 4Material Science, 5Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, USA; 6Institute of Photonics, Dept. of Physics, University of Strathclyde, Glasgow, UK

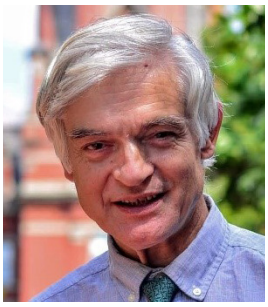
Purpose: Prosthetic visual acuity is limited by the pixel size and by crosstalk from the neighboring electrodes. Acuity better than 20/200 necessitates pixels below 50μm, and local returns are required for the crosstalk suppression. However, small bipolar pixels over-constrain the field penetration and thus limit the efficacy of retinal stimulation. Pre-charging of the electrodes increases the photodiode conductance and thereby can convert the pixels into transient returns. We explore this approach for dynamic confinement of electric field in the retina to achieve high acuity by spatiotemporal control of the images projected onto the photovoltaic array.

Methods: The electric field in the retina generated by a photovoltaic subretinal implant with 821 hexagonal monopolar pixels of 40μm in pitch was modeled using the finite element method, linear combination of the elementary electric fields, and the circuit dynamics of the photovoltaic pixel array in the multidimensional form. Electric fields predicted by the model were compared to the potential mapped by a micropipette ex-vivo, as well as that recorded from cornea in implanted rats. Contrast of the prosthetic vision was modeled for various stimulation schemes.

Results: Spatiotemporal modeling shows that electric current generated by active electrode elevates the potential on neighboring dark pixels and thereby increases their conductance, transforming them into transient returns that suppress the crosstalk without over-constraining the electric field. The distance between the active electrode and the transient return defines the penetration depth of the electric field into tissue. Electric potential recorded ex-vivo matches the model prediction, confirming the effect of the transient return. Due to this effect, contrast in the alternating grating pattern was sufficiently high to achieve acuity matching the 40μm pixel pitch, while with 20μm pixels, it was limited by their natural resolution of about 27μm. For practical applications, multiplexing the images into sparser subframes, together with the effect of transient returns, should enable single-pixel resolution with a contrast of up to 100%.

Conclusions: Spatial coupling of the electric potential between electrodes in electrolyte enables preconditioning the photovoltaic pixels to transform their active electrodes into transient returns for crosstalk suppression. Such optical current steering enables a flexible control of the lateral and axial confinement of electric field, enabling high-contrast prosthetic vision with resolution matching the pixel size.

Biography: Zhijie "Charles" Chen is a Ph.D. candidate in Electrical Engineering at Stanford University, advised by Prof. Daniel Palanker. As an aspirant to restoration of sight with photovoltaic subretinal prosthesis, he designs, models and characterizes the electro-neural interface to optimize the efficacy and selectivity of neural stimulation with multi-electrode arrays. His previous research experience was in wireless communications and signal processing. He finished his bachelor's degree in EE and Economics from Tsinghua University in 2017, and the master's degree in EE from Stanford University in 2019. Charles was a recipient of the Enlight Foundation Graduate Fellowship, Stanford Creativity in Research Scholar, and participant of the Physics Olympiad.



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Hand-Eye Coordination in Virtual Reality under Simulated Ultra Low Vision Conditions

Dagnelie, Gislin; Kartha, Arathy; Sadeghi, Roksana; Lee, Soo Hyun; Swanson, Thom; Gee, Will
Purpose: To develop calibrated measures of hand-ey e coordination for ULV individuals in virtual reality (VR), allowing objective quantification of visual ability in realistic activities of daily living (ADLs).

Methods: Based on an inventory of ADLs valued by ULV individuals (Adeyemo et al., TVST2017) and prior data from visual information gathering ADLs in VR (Kartha et al., ARVO2019/2020), we created 20 scenes with hand-eye coordination ADLs; examples include locating and flipping a light switch, giving a high five to an avatar, picking up common objects, building a block tower, sorting pills, putting on a mitt, and baking cookies and a pancake. Most scenes were implemented at three visibility levels by varying contrast or size, for a total of 55 activities. Scenes were presented in a VivePro Eye VR headset using a Leap Motion hand tracker to visualize the subject's hand. Subjects were allowed to practice manipulating objects in normal vision (NV). Simulated ULV (sULV)was achieved in these normally sighted subjects through Bangerter foils, reducing visual acuity to 2.0 LogMAR. Performance was compared across observers and across vision status (NV vs. sULV).

Results: All four subjects were able to complete 98% of activities in NVand 81% in sULV. Completion times in NV were 4.0 s [2.0,9.7] (median [IQR]), in sULV 6.4 s [3.7,17.8]; 67% of completed activities required (on average 33%) more time in sULV than in NV, with 20 of 55 requiring significantly more time (by ANOVA): Rank correlations of completion times between NVand sULV within observers ranged from 0.62 to 0.71, suggesting that task difficulties were unequally affected by vision degradation. Rank correlations between observers ranged from 0.81 to 0.89 for NV, and from 0.65 to 0.89 for sULV, suggesting subjects were unequally affected, despite equal vision degradation levels.

Conclusions: Most of these activities, representative of ADLs valued by individuals with ULV, could be completed by individuals with sULV equivalent to 20/2000. The wide range of completion times in sULV suggests that these activities cover a broad difficulty range, required to cover the full spectrum of ULV. They will be validated in our population with ULV due to a wide variety of conditions.

Biography: Gislin Dagnelie, Ph.D., is an Associate Professor of Ophthalmology in the Johns Hopkins University School of Medicine and the Associate Director for Research of the Lions Vision Research and Rehabilitation Center, a division of the Wilmer Eye Institute. His work over the last 25 years has been supported by grants from the National Institutes of Health and multiple other public and private sponsors. Dr. Dagnelie was the Center Principal Investigator for clinical trials of the Second Sight Argus™ II retinal implant (2007-2020) and is leading several follow-up engineering studies to make Argus II use more productive in patients' daily lives. He currently participates in the Chicago-based intracortical visual prosthesis (ICVP) project seeking to restore some vision to the blind, for which his laboratory designed phosphene mapping and psychophysical assessment strategies. He is leading the development of assessment and rehabilitation methods for visual prosthesis wearers and other individuals with ultra-low vision, using visual functioning questionnaires and functional vision activities in virtual reality.

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Orion Visual Cortical Prosthesis System: Long-Term Clinical Trial Results

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1Second Sight Medical Products, Inc.
2University of Texas Southwestern 3University of Pennsylvania
4Alfred E. Mann Foundation
5University of California, Los Angeles

Purpose: To evaluate the Orion Visual Cortical Prosthesis System in an early feasibility clinical trial.

Methods: This is a five-year early feasibility study (clinical trials.gov NCT03344848) of subjects who are bilaterally blind with bare light or no light perception due to non-cortical etiology. The main objectives are to evaluate the safety of placing and activating an electrode array on the medial surface of the occipital lobe in blind patients; to evaluate the functionality of the device; to perform research to study the nature of the vision provided by the Orion; and to obtain input for future device design.

The Orion System comprises an implant (consisting of an electronics package, receiving antenna, and an electrode array with 60 non-penetrating electrodes); glasses with a video camera; headwear containing a transmitting antenna; and a video processing unit (VPU). The video camera collects real-time visual information, which is then processed by the VPU and converted to stimulation patterns on the electrode array. A radio frequency link between the transmitting and receiving antenna sends data and power to the implant.

The study is a prospective, non-randomized, single-arm trial with six subjects at two centers, UCLA and Baylor College of Medicine. Safety is evaluated with rates, relatedness, and seriousness of adverse events, which are collected throughout the study. Performance is assessed at 6 months, 12 months, 24 months, and 36 months with the Functional Low-vision Observer Rated Assessment (FLORA), visual function tests, and patient-reported outcomes.

Study visits were paused at both centers in March 2020 due to the COVID-19 public health emergency. Visits were subsequently resumed in September 2020 at UCLA and December 2020 at Baylor.

Results: Five males and one female were implanted between January 2018 and January 2019. As of April 1, 2021, average implant duration was 34.1 months (range 26.5 – 38). Average age at time of implant was 48.6 years. All subjects had bare or no light perception at the time of implant but were previously sighted. Causes of blindness included trauma, endophthalmitis, and pediatric glaucoma.

The Orion was implanted successfully in all six subjects. One serious adverse event due to the device (seizure) has been reported; 13 non-serious adverse events due to the procedure or device were reported.

As of April 1, 2021, performance had been evaluated for all six subjects at the 12-month time point, and performance had been evaluated for five subjects at the 24-month time point. Results between these follow-up periods were consistent, with 83% (12 months) - 100% (24 months) of subjects performing significantly better with the Orion System turned ON than OFF on Square Localization, a test of light perception/projection. On Direction of Motion, a spatial vision test, 100% - 80% of subjects performed significantly better ON than OFF; and on Grating Visual Acuity, 50% - 40% were able to score on the visual acuity scale with the System ON. Subjects were rated as having experienced positive or mild positive benefit from the Orion in their every-day lives at both time points (83% - 100%).

Performance is now being evaluated at three years post-implant for several Orion subjects. These data will be presented and compared with earlier time points.

Conclusions: The first-in-human clinical trial of the Orion Visual Cortical Prosthesis has demonstrated the feasibility of safely creating some artificial vision via subdural stimulation of the visual cortex with a fully-implanted chronic visual prosthesis. Long-term (over 2 years) safety and performance data are very promising in this small early feasibility study.

Biography: Dr. Dorn joined Second Sight Medical Products in November 2006. As Vice President of Clinical and Scientific Affairs, she leads the effort to understand and improve the artificial vision created by the Orion and Argus II Systems. Her work encompasses clinical research strategy, clinical trial design and management, low vision outcome measures, and human visual psychophysics. She received her Ph.D. in Neuroscience from UCLA, studying primate visual cortex, and her B.A. in Biology from the University of Chicago.

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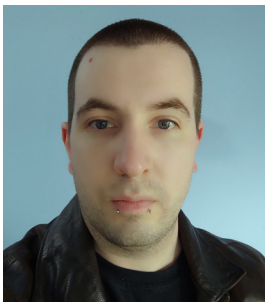

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Photochemical Damage Implications to Optogenetic Forms of Cortical Prosthesis

John Exton, Ethan Cohen, Patrick Degenaar, Jinju Chen, Andrew Trevelyan

Purpose: Optogenetics has demonstrated some potential advantages as a method for modulating neural activity; it is minimally mechanically invasive, capable of dual colour excitation/inhibition and has the capacity for specific targeting of neural subpopulations. Photons in the blue end of the spectrum can cause photochemical damage. As such, there is regulatory guidance available as to the irradiance which can be imparted on the retina within any 10e4s period [1]. Early examination of these regulations showed that blue light stimulation safety was borderline depending on the duty cycle and stimulus requirement [2].

Optogenetics utilizes three common wavelengths: 470nm, 532, 590nm eq. The former has been shown to be capable of causing photochemical damage in the retina depending on duty cycle and stimulus requirement [1], with longer wavelengths being safe. Whilst thermal damage from optical stimulation has been explored in cortical tissue [3], there is currently no photochemical damage per time equation for cortical cells. Since retina is chronically exposed to ambient broadband light it possesses enzymatic and chemical protective mechanisms against blue light that may be reduced or absent in cortical tissue. Thus, it is important to determine safe thresholds of cortical illumination for these common wavelengths.

Methods: We have examined the relationship between photochemical damage threshold and irradiance in rodent brain slices using 470 and 565nm light at irradiance values 2-5X above those used for cortical stimulation. 400µm diameter optical fibres were used, with an exposure time of 30-180 mins. Apoptosis and DNA fragmentation were determined using TUNEL staining, and slices were imaged using confocal microscopy.

Results: Preliminary data suggest blue light is significantly more toxic to cortical neurons in slices than orange light.

Conclusions: Optogenetic experiments may need to examine more precise toxicity thresholds and mechanisms with wavelength in cortex and study these thresholds in-vivio.

Biography: John Exton is a Ph.D. student in Mechanical Engineering at Newcastle University, England. He works with Dr. Jinju Chen and Prof. Jonathan Higgins on mechanical properties of brain tissue and is engaging in a collaborative study with Prof. Patrick Degenaar and Prof. Andrew Trevelyan on optical toxicity in brain. He holds an M.Sc. in Biomedical Science from the National University of Ireland, Galway and finished his B.Sc. in Biomedical Science at Durham University in England.

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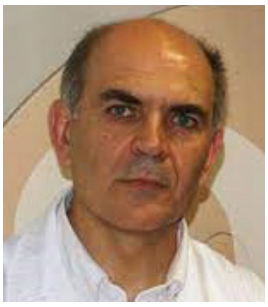

Eduardo Fernandez, M.D., Ph.D.
University Miguel Henandez
Elche, Spain

Visual Percepts Evoked with an Intracortical 96-channel Microelectrode Array Inserted in Human Occipital Cortex

Eduardo Fernández. University Miguel Hernández and CIBER-BBN, Spain.

Purpose: A long-held dream by scientists has been to directly transfer information to the visual cortex of blind individuals, to restore a rudimentary form of sight. We have proposed that arrays of penetrating electrodes such as the Utah Electrode Array (UEA), might form the foundation for the restoration of a useful visual sense. However, a number of questions remain regarding the use of the UEA for a cortical visual prosthesis. Our main goal is to answer some of these questions and to present updated results regarding electrical stimulation of the visual cortex in a long-term blind volunteer.

Method: We implanted an intracortical microelectrode array (consisting of 96 electrodes) in the right visual cortex of a 57-year-old adult with complete blindness over the past 16 years, for a six-month period. The primary outcome measures were current thresholds and characteristics of the visual percepts elicited by intracortical microstimulation.

Results: Implantation and subsequent explantation of intracortical microelectrodes were carried out without complications, and we successfully evoked phosphenes on 88 of 96 electrodes using electrical stimulation. The mean stimulation threshold when using single electrodes was 66.8 36.5 A, which was within the safe range for neural stimulation. We consistently obtained high-quality recordings from visually deprived neurons throughout the duration of implantation and found that both the recorded neural activity and the stimulation parameters remained stable over time. Furthermore, simultaneous stimulation via multiple electrodes were associated with a significant reduction in thresholds ($p<0.001$, ANOVA test) and evoked discriminable phosphene percepts, allowing the blind participant to identify letters and recognize object boundaries. Finally, we observed a learning process that helped the subject to recognize these complex patterns over time.

Conclusions: Our results show that a multielectrode array of 100 penetrating electrodes is able to safely generate phosphenes for many months and that multiple electrode stimulation evokes discriminable patterned perceptions that allow the identification of some letters and well as to recognize object boundaries. These findings support our earlier findings in monkey experiments, demonstrate the safety and efficacy of chronic intracortical microstimulation via a large number of electrodes in human and suggest that several arrays of penetrating electrodes might form the basis for a cortically based solution for sight restoration in individuals with profound blindness.

Biography: Dr. Fernandez received a M.D. degree from the University of Alicante (1986) and a Ph.D. in Neuroscience with honors in 1990. He is currently Professor and Chairman of the Department of Histology and Anatomy of the University Miguel Hernández (Spain), Director of the Neural Engineering Group of the Centro de Investigación Biomédica en Red (CIBER) in the subject area of Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN, Spain), and Adjunct Professor at John Moran Eye Center (University of Utah, USA). He is a qualified MD who combines biomedicine (molecular and cellular biology, biochemistry, anatomy, physiology and regenerative medicine) with the physical sciences and engineering to develop innovative solutions to the problems raised by interfacing the human nervous system. In the latest years he has been coordinating several projects to demonstrate the feasibility of a neuroprosthesis interfaced with the occipital cortex as a means through which a limited but useful sense of vision could be restored to profoundly blind. He is also working on brain plasticity and reorganization in severe vision loss and developing non-invasive methodologies for the selection of appropriate candidates for the implantation of a cortical visual prosthesis.

Shelley Fried, Ph.D.
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Towards the Development of a Micro-coil Based Cortical Visual Prosthesis

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2Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
3Department of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, USA

Purpose: We are developing a cortical visual prosthesis that uses implantable micro-coils instead of conventional micro-electrodes. The use of magnetic stimulation to drive cortical neurons is attractive because the induced fields from micro-coils are spatially asymmetric and therefore, can be harnessed to selectively target or avoid specific neuronal sub-populations. For example, implanted coils can activate local pyramidal neurons while avoiding activation of passing axons, thus confining activation to a focal region. Also, because there is no direct contact between coils and cortical tissue, many of the stability concerns associated with implantable micro-electrodes can be avoided.

Methods: We ran a series of experiments using behavioral testing in rats to further evaluate the stability of chronically implanted micro-electrodes. A series of computational models along with in vitro and both rodent and NHP in vivo experiments have been used to evaluate the efficacy of magnetic stimulation. Computational models help to identify the coil features that underlie sensitivity and selectivity while in vitro experiments are used to evaluate and compare different coil designs. In vivo rodent experiments measure cortical surface activity (ECoG) in response to magnetic (or electric) stimulation; a custom-designed 128-channel recording array is positioned on the surface of visual cortex (V1) and captures the spread of activation in response to stimulation from a micro-coil (or micro-electrode) inserted through a hole in the center of the recording array. In vivo NHP behavioral experiments will use a detection task to determine stimulation thresholds in micro-coils.

Results: Chronic implantation of micro-electrodes into S1 revealed changes in threshold over the course of implantation with some variability depending upon which layer was stimulated. Acute testing of magnetic and electric stimulation (implanted into V1, layers 2/3 and 5) both elicited strong surface (ECoG) responses, although the area activated by micro-coils was confined focally within a ~300-m in diameter region, and that of micro-electrodes was more spatially expansive, often extending more than 1-mm from the stimulation site. In vitro testing of human cortical tissue (resected during medically-necessary neurosurgical procedures) revealed comparable sensitivity of individual neurons in both species. Psychophysical testing in non-human primates has commenced, with encouraging preliminary indications that the animal can detect magnetic stimulation from micro-coils acutely implanted in V1.

Conclusions: Our results continue to support the viability of micro-coils as an effective alternative to conventional micro-electrodes. The focal magnetic activation from micro-coils in rodent in vitro and in vivo experiments supports the notion that distinct, focal phosphenes can be created that will summate to produce more spatially-complex percepts. Psychophysical testing in NHPs will be necessary to determine whether elicited percepts are indeed more focal with magnetic versus electrical stimulation as expected.

Funding: Research supported by the NIH (NINDS U01-NS099700 and NEI R01-EY029022 / EY023651) and by the Dept. of Defense / CDMRP (VR170089), and the William M. Wood Foundation, Bank of America, Trustee.

Biography: Shelley Fried is the Director of the Neural Prosthetic Research Laboratory at the Massachusetts General Hospital and an Associate Professor in the Department of Neurosurgery at Harvard Medical School. He holds a Ph.D. in Vision Science from UC Berkeley and did postdoctoral training at the Massachusetts General Hospital in Boston studying electric stimulation of the retina. His lab studies artificial stimulation of the CNS, focusing on the mechanisms underlying neuronal responses to artificial stimulation as well as on the development of more effective stimulation strategies and devices.

Fabrizio Grani, M.Sc.
University Miguel Hernandez
Elche, Spain

Development of a Closed-loop Approach for Automatically Adjusting Thresholds in Cortical Visual Prostheses

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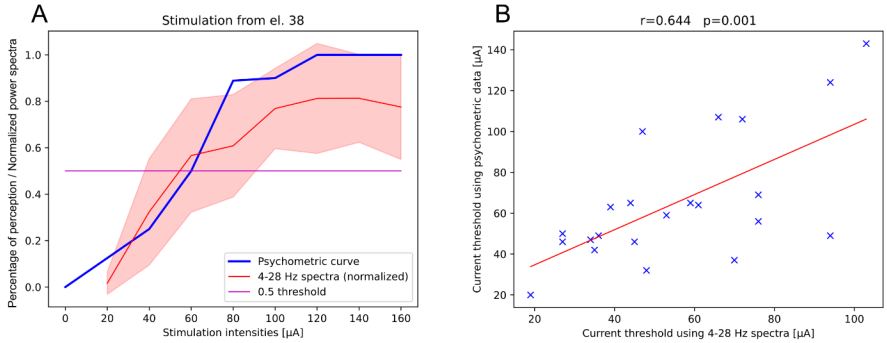
Purpose: Cortical visual prostheses are a potential method to restore vision in profoundly blind people. An effective cortical prosthesis may include thousands of electrodes and prospective users need to adjust the thresholds individually for each single electrode. This process is time consuming, and users might experience fatigue during the determination of thresholds. Our main goal is the development of an automated procedure, based on neural recordings, to adjust stimulation thresholds without the need of patient interaction.

Method: We implanted an intracortical microelectrode array (consisting of 96 electrodes) in the visual cortex of a 57-year-old adult with complete blindness. Standard psychometric experiments with different stimulus amplitudes, ranging from 1 to 160 □A, were performed with simultaneous electrophysiological recordings during electrical stimulation for a 6-month period. After removing the electrical artifacts recorded on the electrode array, we extracted the sum of 4-28 Hz spectra components of the recordings during the stimulation and analyzed how these spectra changed with stimulation intensity obtaining a curve that we compared with the standard psychophysics curves based on subject answers. We assumed as perception threshold the stimulation intensity at which the subject reported to see a phosphene 50% of the time, and we compared this intensity, to the stimulation intensity at which the 4-28 Hz spectra curve reached half of his maximum.

Results: The normalized 4-28 Hz spectra correlates with the standard psychometric curves obtained with the subject answers (mean r=0.85). The automated thresholds obtained with the proposed closed-loop approach, without the need of subject interactions, correlated well (r=0.64, p=0.001) with perception thresholds obtained with the subject answers.

Conclusion: Our results showed that neural recordings provide direct insight into the efficacy of stimulation. Although more studies are still needed, our results suggest that the 4-28 Hz signal spectra contains information related to perception and can be used to automatically estimate current thresholds.

Biography: Fabrizio Grani received a bachelor's degree in Biomedical Engineering from Università di Pisa in 2016 and a master's degree in Bionics Engineering with specialization in Neural Engineering from Università di Pisa and Scuola Superiore Sant'Anna in 2019. After working as a research engineer in Medel (Innsbruck), he joined the group of Eduardo Fernandez at Universidad Miguel Hernández de Elche as a Ph.D. student. He is currently working on the development of a cortical visual prosthesis based on Utah Electrode Array, with a particular focus on signals analysis for the optimization of the stimulation strategy for phosphenes perception.



A) Example of normalized 4-28 Hz spectra and standard psychometric curve. B) Relation between perception threshold found with the proposed approach and the subject answers.

Justin Kasowski, B.Sc.
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Immersive Virtual Reality Simulations of Bionic Vision

Justin Kasowski, Nathan Wu, Michael Beyeler University of California, Santa Barbara

Purpose: A major outstanding challenge in the field of bionic vision is predicting what people "see" when they use visual prostheses. Studies of simulated prosthetic vision (SPV) often simplify phosphenes into small independent light sources – despite recent evidence suggesting that phosphenes vary drastically across subjects and electrodes. In addition, real bionic eye recipients use head movements to scan the scene, which is difficult to simulate on a computer screen. To address these challenges, we embedded biologically realistic SPV models in immersive virtual reality (VR) so that sighted subjects could act as virtual patients in real-world tasks.

Methods: The external camera of a visual prosthesis was simulated by tracking head movements of a VR headset using the Unity game development engine. The field of view matched those experienced in real devices. Electrode activations were determined by averaging the brightness across a representative area of the screen. A psychophysically validated SPV model was used to determine the shape of each phosphene based on the stimulus parameters as well as the retinal location of the simulated implant. This allowed for realistic phosphene predictions of both epiretinal and subretinal implants.

Results: We were able to simulate epiretinal implants with up to 600 electrodes and subretinal implants with over 1600 electrodes at 60 Hz using an NVIDIA RTX 2070 Super. The world successfully updated with head movements and could be used with both virtual and augmented reality, allowing virtual patients to perform virtual versions of tasks typically performed by prostheses developers, such as square localization, letter recognition, and door finding.

Conclusion: This work constitutes a first essential step towards immersive VR simulations of bionic vision, taking into account a user's head (and in future work eye) movements as they explore an immersive virtual environment. The system has been optimized to run in real time and can be modified for various phosphene models as well as thalamic and cortical implants.

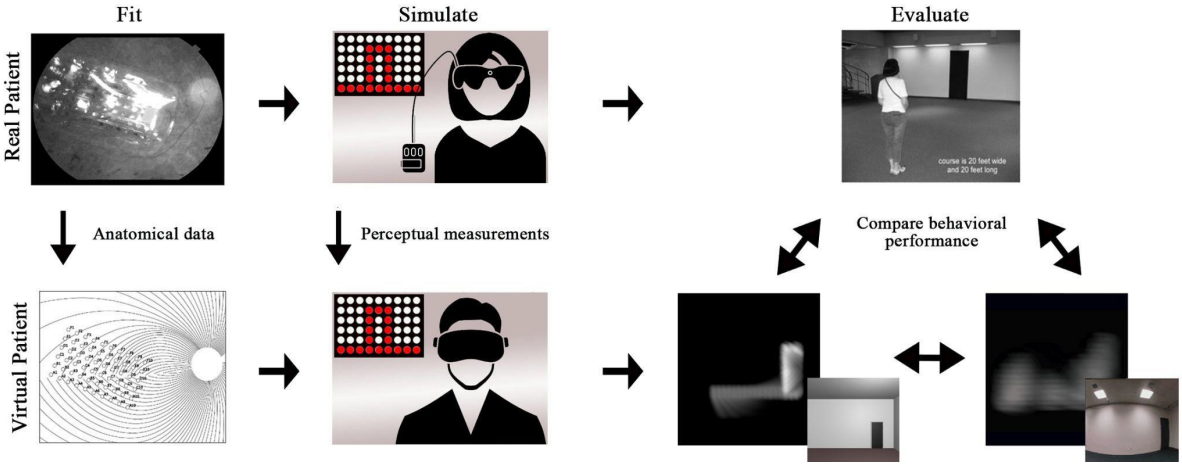

Fig. 1: Virtual and real patients for bionic vision. Top: Real patient performing a door locating task. Bottom: Simulated device created by matching anatomical and perceptual measurements from real patients being used to perform virtual and augmented reality versions of the same task

Biography: Justin Kasowski is a Ph.D. Candidate in the UCSB: Dynamical Neuroscience program. He works in the Bionic Vision Lab creating and validating neuroanatomically correct models for prosthetic vision. Through validated models, he is able to test novel preprocessing methods and device configurations with the ultimate goal of restoring vision to the blind.

Seong-Woo Kim, Ph.D.
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Seoul, Korea

Effects of Different Subretinal Implant Designs on the Retina in Mini-pigs and Drug Induced Incomplete Outer Retinal Degeneration in Cynomolgus Monkey

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Purpose: I presented the research works of the Korea consortium for retinal prosthesis development performed last year for the development of retinal prosthesis.

First topic is about the retinal changes caused by various three-dimensional (3D) microelectrodes implanted subretinally based on implant geometry in mini pig. Second topic is about in-vitro and in-vivo assessment of drug-induced outer retinal degeneration model in non-human primate.

Method: First, to evaluate the influence of subretinal 3D microelectrodes and substrate on the ovelying retina, we designed some variations on the geometry of the implant.

In the preliminary experiment, 75 μm-tall 3D electrodes on a 200 μm-thick right-angled polydimethylsiloxane (PDMS) substrate (group 1, n=3) and dome-shaped 40 μm-tall 3D electrodes on an 18 μm-thick parylene-C substrate (group 2, n=3) were implanted in the subretinal space of mini-pig. In the second experiment, a 140 μm-thick sloped PDMS substrate without electrodes (group 3, n=3) and with 20 μm-tall 3D electrodes (group 4, n=3) were implanted into the subretinal space of mini-pig, and 1 female mini-pig was used as a control for immunohistochemistry during examination. In all experiments, spectral-domain optical coherence tomography (SD-OCT) images were obtained at baseline and 2, 6, and 12 weeks after surgery.

Second, to develop drug induced outer retinal degeneration disease model in cynomolgus monkey, we filled the vitreous cavity temporarily with the N-methyl-N-nitrosourea (MNU) during vitrectomy. Then after confirming the degree of outer retinal degeneration with various morphological and functional tests, we tested the custom-made 2D and 3D electrodes if subretinally positioned electrodes could evoke RGC spikes in in vitro (ex-vivo) monkey RP model.

In 5 cynomolgus monkeys, 2 mg/ml MNU (case #1), 2.5 mg/ml MNU (case #2 & #3), or 3 mg/ml MNU (case #4 & #5) was temporary loaded for about 10 minutes and washed out with balanced salt solution (BSS) at the end of vitrectomy. Multimodal examinations including SD-OCT images, visual evoked potentials (VEP) and full-field electroretinography (ffERG) were obtained at baseline and week 2, week 6, and week 12. At 12 weeks, histologic examination (n=3) and multielectrode array (MEA) examination (n=2) was performed after sacrifice of animal. For MEA assessment of RP model, eyeballs were enucleated and retinas were isolated for the MEA recordings of RGC spikes. For the control, electrical stimulation from epiretinal side were applied to the retinas from non-MNU treated eyeballs to evoke RGC spikes. Biphasic current pulse amplitude and duration were modulated (1~200 A, 0.1 ms ~ 4 ms). Our custom made 256 pixels 2D Platinum (Φ: 90 um) or 3D Iridium (Φ: 26 um) electrodes were positioned subretinally, then electrical stimulation through these electrodes were applied and RGC spikes were recorded conventional 8*8 MEA. We isolated two different regions of retinas for MEA recording, fovea and perifovea regions since fovea and perifovea show different RGC density.

Result: In the 3D electrodes and substrates study, 3D electrodes of group 1 touched the inner plexiform layer (IPL) directly, and severe fibrous reaction was noted around the implant over time on OCT. On the other hand, in implants of groups 2, 3 and 4, the foreign materials remained in place without migration under the retina (Figure 1). Except group 1, retinal ganglion cells and bipolar cells were preserved intact without fibrosis over the retinal implants in immunostaining results in remaining 3 groups during the implantation period of 12 weeks.

In the outer retinal degeneration animal model study, mean age of the monkey was 52.47±6.86 months. Mean body weight was 3.82±0.48 kg. In all cases, fellow eyes showed no significant change in OCT and electrophysiology tests at follow-up periods. Incomplete outer retinal degeneration was induced in four eyes, and phthisis bulbi occurred in case #5 (3mg/ml). Among four eyes with outer retinal degeneration, OCT of case #1 and case #2 showed outer retinal layer loss (outer plexiform layer ~ photoreceptor outer segment) in the peripheral retina and relatively preserved retinal layer in the posterior pole of the eye although case #2 (2.5mg/ml) presented more severe ellipsoid zone loss in posterior pole than that of case #1 (2mg/ml). In OCT of case #3 and case #4, peripheral retinal thinning was so severe that it was very difficult to differentiate each layer of the remaining retina. Even in the post pole, inner retinal damage was observed in addition to the outer retinal loss. The degree of damage was more pronounced in case #3 (2.5 mg/ml) than in case #4 (3mg/ml). Complete fovea atrophy was noted in case #3. Mean thickness of total retina, inner segment, and outer segment of the retina seemed to be stationary from week 2 to week 12. In the incomplete outer retinal degeneration cases, while VEP responses were relatively preserved, the ERG showed the loss of rod responses and the decrease of cone response. So incomplete outer retinal degeneration cases were complete rod cell loss with partial preservation of cone cell.

In the MEA recording (case #1 and #3), with our custom-made 2D and 3D electrodes, RGC spikes were also evoked both in non-MNU treated and MNU treated retinas. Perifovea regions (n=2) showed better modulation curves than fovea regions (n=1). RGC spike response curves are better modulated with 3D electrodes (n=2) than 2D electrodes (n=2).

Conclusion: The analysis of four different designs of subretinal implants showed differences in the degree of reaction in the retinal tissue. A sloped substrate yielded better results than a right-angled substrate for preserving the retina over the implanted electrodes. Furthermore, the height and the shape of the 3D electrodes should be decided based on the target retinal neural cell location in the retina considering the thickness of the target layer itself and remaining retinal thickness below the target layer together. In the second study, temporal MNU loading in a vitrectomized cynomolgus-eye model could induce incomplete outer retinal degeneration, and our custom-made 2D and 3D electrodes worked to evoke RGC spikes in in-vitro retinas. The number of retinas we used are not enough for quantitative analysis such as regional difference of RGC response, 2D and 3D electrodes comparison. Therefore, here we only report qualitative differences.

Biography: Seong-Woo Kim M.D, Ph.D., graduated Korea University College of Medicine and took Ophthalmology resident training and retina fellow training in Korea University Guro Hospital. He was appointed as assistant professor in 2008 at the Korea University and has been a professor since 2017 in the same university.

As an active retinal surgeon and clinician, he is a retina section chief of Korea University Guro Hospital. He performed more than 4,200 cases of vitrectomy and buckling surgery since 2006 for diabetic retinopathy, retinal detachment, and various macular diseases. He has been involved in the various international multicenter clinical studies and currently actively participating in the six multicenter clinical studies including VEGF traps intravitreal injection (Bayer, Samsung bioepis) and others.

As a researcher, he has published 80 SCI(E) papers regarding retinal diseases and basic research. He visited Institute for Ophthalmic Research of Tuebingen University as a visiting scholar and participated in the animal experiment during Aug 2014~Aug 2015 under Prof E. Zrenner. In 2016, he received the national research grant for individual researcher regarding retinal prosthesis development and recruited the researchers who were excellent in his or her own research field in Korea for retinal prosthesis development. After he and his team successfully won the competition for the national research grant for retinal prosthesis development ($4,000,000) in 2017, the team concentrated on the retinal prosthesis R&D. On his team, Professor Kim's role is to perform animal experiments to test efficacy and safety of the implant. Professor Seong-Woo Kim has developed various kinds of drug induced outer retinal degeneration animal models in the rabbit, dog, mini-pig, and non-human primate (cynomolgus monkey) using vitrectomy and drug exposure. In 2020 he received another national research grant for individual researcher regarding drug induced animal model development in non-human primate. He is now a deputy director of animal research center of Korea University Guro Hospital and an editorial board member of Scientific Reports journal and Journal of Retina (official journal of Korean Retina Society).

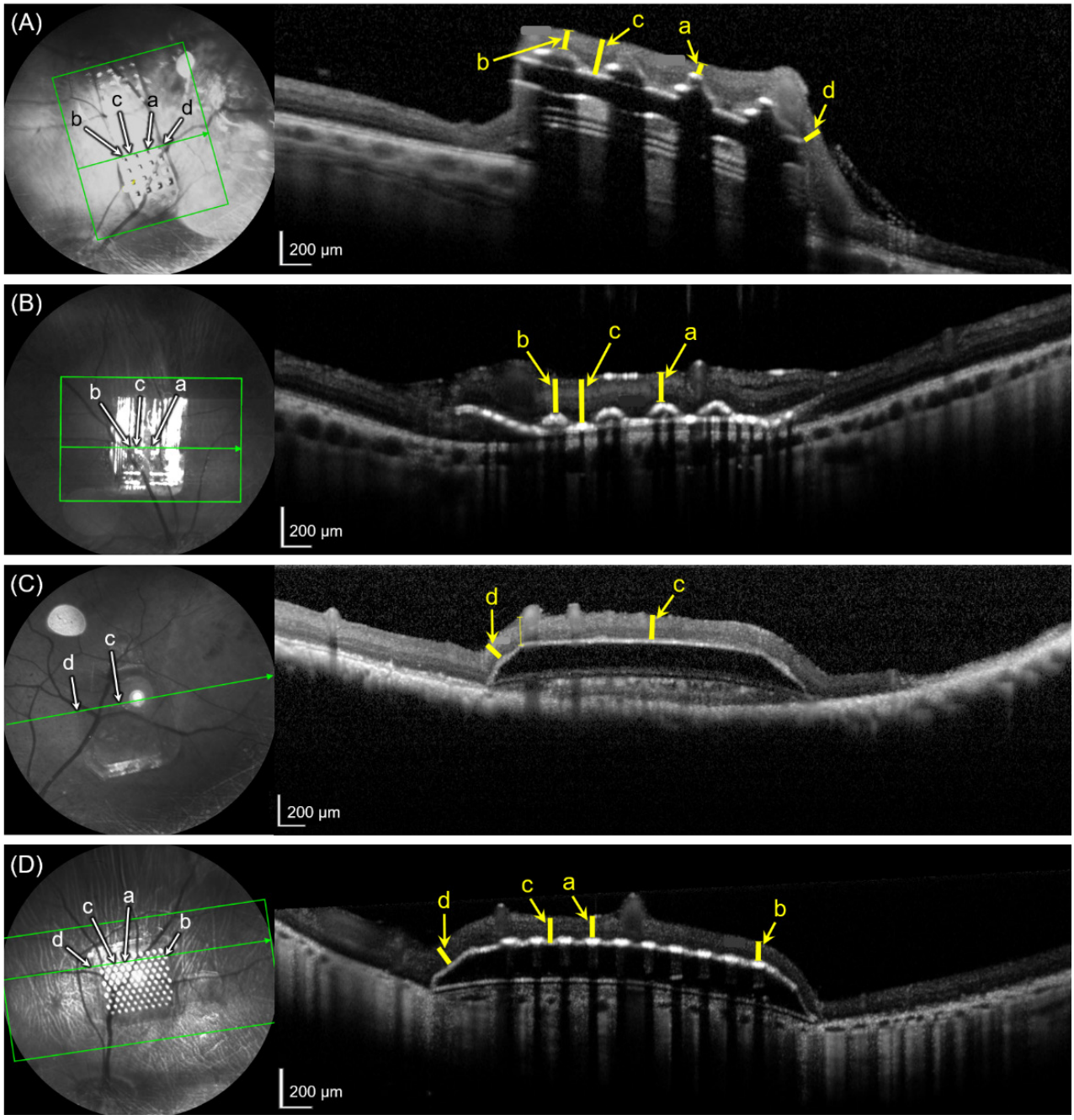

Figure 1. Total retinal layer (TRL) thicknesses including the TRL thickness over the electrode (a: center location, b: marginal location) and TRL thickness over the substrate (c) and at the edge (or slope) of the substrate (d) were measured in (A) group 1, (B) group 2, (C) group 3 and (D) group 4. The TRL thickness over the electrodes (a, b) was defined as the perpendicular distance between the center of each electrode and the inner margin of the internal limiting membrane. The TRL thickness over the substrate (c) was defined as the perpendicular distance between the surface of substrate (the center points of 2 adjacent electrodes) and the inner margin of the internal limiting membrane. The TRL thickness at the edge or slope of the implants (d) was defined as the perpendicular distance between the edge or sloped surface of the substrate and the inner margin of the internal limiting membrane.

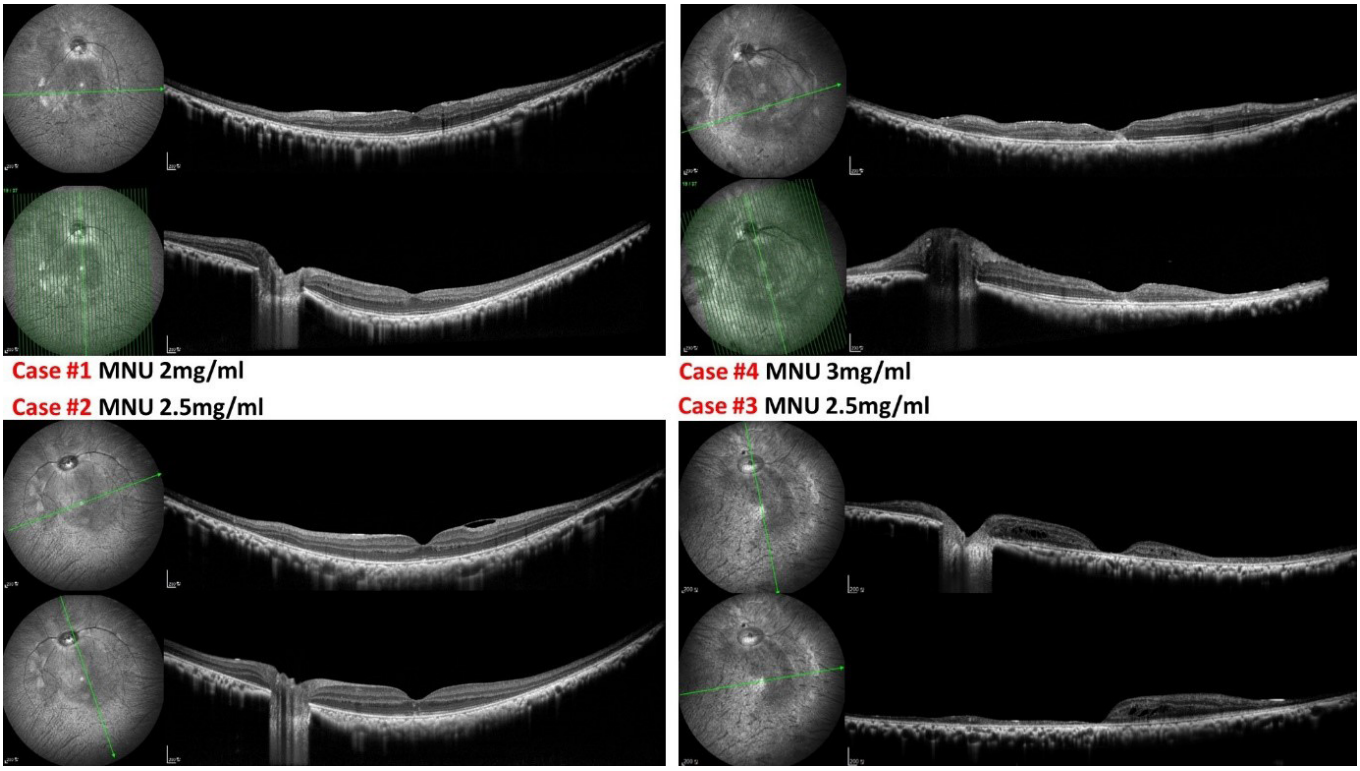

Figure 2. By increasing the MNU concentration, retinal degeneration was getting severe. But there was also overlapping of degeneration degree between each MNU drug concentration. The order of retinal degenerative degree was case #1 (2mg/ml), case #2(2.5mg/ml), case #3 (3mg/ml), case #4 (2.5mg/ml), and case #5 (3mg/ml). OCT image of case #5 could not be acquired because of the phthisis of bulbi.

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Long Term Visual Results of Prima Chip in Patients with Geographic Atrophy

Y. Le Mer, R. Hornig, G. Buc, S. Mohand-Said, J.A. Sahel, D. Palanker

Purpose: To evaluate the long-term central prosthetic vision with the photovoltaic subretinal implant activated by augmented-reality glasses and simultaneous perception of the natural peripheral vision in patients with geographic atrophy.

Methods: Five patients with visual acuity ≤20/400 due to geographic atrophy of at least 3 optic discs diameters and no foveal vision have been implanted with a wireless photovoltaic chip (PRIMA, Pixium Vision) of 2x2mm in size, 30μm in thickness, containing 378 pixels of 100μm in width. Each pixel in the implant converts pulsed near-infrared light (880nm) projected from video glasses into electric current to stimulate the nearby neurons in the inner nuclear layer of the retina. Prosthetic acuity was assessed using electronic magnification of 1, 2, 4 and 8. Simultaneous perception of central prosthetic and peripheral natural vision was evaluated under room lighting.

Results: In all patients, chip implanted under the macula remained stable and functional. One patient passed away after 18 months, and the four others have a follow-up extending now up to three years. No decrease in natural eccentric visual acuity was observed in any of the study eyes. All five patients could perceive white-yellow patterns with adjustable brightness, in retinotopically correct locations within previous scotoma during the follow-up period. Among the four remaining patients, two patients with correct subretinal placement of the chip achieved Snellen visual acuity without zoom of 20/438 to 20/564, after 18-30 months. With electronic magnification of up to a factor of eight, three patients demonstrated acuity in the range of 20/63-20/98. Under room lighting, patients could simultaneously use prosthetic central vision and the remaining peripheral vision in the operated eye and in the fellow eye. We'll present the three years results, the patients being allowed to come back to hospital for testing at the end of the French lockdown in June.

Conclusions: Wireless chip PRIMA implanted under the atrophic macula in patients with geographic atrophy remains stable and functional during the three years of follow-up. The implant provides central visual perception with acuity close to the single pixel size of the photovoltaic array. Augmented reality glasses enable simultaneous perception of the central prosthetic and natural peripheral vision under room lighting, while electronic zoom provides significantly higher resolution.

Financial disclosures: Y. Le Mer: consultant with Pixium vision; R. Hornig : Medical director Pixium Vision; G. Buc, Technical director Pixium-Vision; JA Sahel : Equity owner at Pixium Vision; D. Palanker: Consultant, Patents and Royalties with Pixium Vision.

Biography: Dr. Le Mer is Head of the department of vitreo-retinal pathologies in the Hospital Fondation A. de Rothschild in Paris, France. He has been working for more than 10 years with Professor J.A. Sahel. Dr. Le Mer created a Clinical Research Unit, oriented towards the evaluation of new treatments for retina diseases. Dr. LeMer was able to work with Pixium-Vision, first with the IRIS I and II systems for retinitis pigmentosa and currently on the PRIMA chip for patients with geographic atrophy during the last six years, and developing surgical techniques for a safe sub-retinal implantation.

Jae-Ik Lee, Ph.D.
Harvard Medical School
Boston, Massachusetts

Mechanisms Underlying Differential RGC Responses to Low vs. High Rate Stimulation

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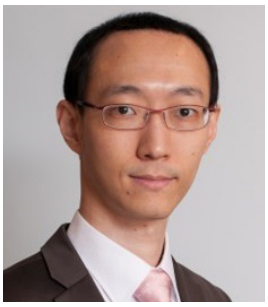
2Institute for Analysis and Scientific Computing, Vienna University of Technology, Vienna, Austria
3Boston VA Healthcare System, Rehabilitation, Research and Development, Boston, MA, USA

Purpose: It has been reported that the response of RGCs to high-rate electric stimulation is non-monotonic, i.e., increasing the amplitude of stimulation initially leads to increases in spiking activity, but subsequent increases cause a decrease in the response. This non-monotonic response pattern is in contrast to responses arising from single pulses or pulses delivered at low repetition rates, which typically follow a monotonic curve. To understand the transition from monotonic to non-monotonic responses, we measured the responses of RGCs to a wide range of stimulus frequencies and explored the underlying mechanisms.

Methods: A sinusoidal electric stimulus (frequencies between 100-2500 Hz, amplitudes 10-100 A, duration of 1 s) was extracellularly delivered to ON-sustained RGCs (n = 10) in the isolated retinas of wild-type mice (C57BJ/6J). The whole-cell patch clamp recording was used to capture both the spiking responses and the changes in membrane voltage. A computational model was then developed to explore the contribution of individual membrane currents to the overall neuronal response.

Results: Testing the complete range of frequencies provided a comprehensive overview of the gradual shift from monotonic to non-monotonic response patterns. We also observed that the baseline membrane potential (Vm) during stimulation could be both depolarized or hyperpolarized depending on the stimulus condition, and, more importantly, the polarization of Vm was strongly correlated with the pattern of spiking responses; stimulus conditions that hyperpolarized Vm also resulted in monotonic spiking responses while those that depolarized Vm also led to non-monotonic spiking patterns. Our computational model showed that the dynamics of voltage-gated ion channels underlies the differential Vm polarization and the response patterns.

Biography: Jae-Ik Lee is an Instructor in the Department of Neurosurgery at the Massachusetts General Hospital, Harvard Medical School in Boston. Dr. Lee has a Ph.D. in mechanical engineering from Yonsei University, South Korea, and did postdoctoral training at both the Henry Ford Hospital in Detroit and the Massachusetts General Hospital in Boston studying electric stimulation of the retina. His research focuses on how and why neurons respond to artificial stimulations, including electric, magnetic, and acoustic stimulations, with the goal of developing improved methods and strategies.



Seung Woo Lee, Ph.D.
Massachusetts General Hospital
Harvard Medical School

Micro-magnetic Stimulation of Primary Visual Cortex (V1) Elicits Focal Activation of Secondary Visual Cortex (V2)

Seung Woo Lee1 and Shelley I. Fried1,2.
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Purpose: Electric stimulation of the primary visual cortex (V1) via implantable electrodes has the potential to restore vision to patients suffering from a wide range of visual impairments. Despite some early success in eliciting visual perception in human subjects, the inability of conventional electrodes to confine activation to a small cortical region raises concerns about the potential effectiveness of such an approach. In addition, the complex biological reactions to implantation may diminish the stability of the electrode-tissue interface. Recent demonstrations that magnetic stimulation from a micro-coil can confine activation to single cortical columns of mouse V1 suggest the possibility that a coil-based approach may overcome some of those limitations. Here we show that the micro-coil based magnetic stimulation of V1 induces focal activation in the secondary visual cortex (V2).

Methods: Single-loop micro-coils based on platinum-iridium (Pt-Ir) flat ribbon wires were fabricated for use in magnetic stimulation; concentric bipolar Pt-Ir electrodes were used for control experiments (i.e., electric stimulation). Calcium imaging (GCaMP6s) using brain slices containing both V1 and V2 (i.e., lateromedial, LM) regions was conducted to evaluate the responses that arise in V2 secondary to stimulation of V1.

Results: Our results revealed that both electric and magnetic stimulation of V1 could activate V1 and that such activation resulted in activation of V2 neurons. However, the activation from micro-coils was confined to a smaller area of V2 than that from bipolar electrodes.

Conclusions: Our findings suggest that magnetic stimulation with micro-coils can enhance the spatial resolution of indirect activation in V2 and thus may lead to more effective cortical visual prostheses.

Funding: Research supported by the NIH (NEI R01-EY029022 / EY023651 and NINDS U01- NS099700) and by the Dept. of Defense / CDMRP (VR170089).

Biography: Seung Woo Lee is an Assistant Professor of Neurosurgery at Harvard Medical School (HMS), and Assistant Investigator in the Neurosurgery at Massachusetts General Hospital (MGH). He received the B.S. degree in school of electrical engineering and computer science from Seoul National University (SNU), Seoul, Korea, in 2003. He received the Ph.D. degree in the school of electrical engineering and computer science from the Seoul National University (Advisor: Prof. Sung June Kim), in 2010. He trained as a Research Fellow from 2011 to 2015 in Dr. Shelley Fried's lab in the Department of Neurosurgery at MGH and HMS. Dr. Lee has extensive experience in neural prosthetics, brain-computer interfaces, retinal implants, cochlear implants, deep brain stimulation, and electrical engineering. His research interests include development of chronic implantable electronic system (BioMEMs and Bioelectronics) as well as effective electric/magnetic neural stimulation strategy (Neurophysiology) for neuroscience research and neural prosthesis.

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Controlling Neuronal Activity of Retinal Ganglion Cells Using Dynamic Frequency Modulation

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Rationale: Kilohertz electrical stimulation (KES) has been previously used to preferentially activate different retinal ganglion cells (RGCs) under idealistic long-duration, and static stimulation conditions. In this study, we investigated the generalizability of this technique with continuous, dynamic stimulation and shorter stimulation durations. The ability to control RGC pathways with more practical stimulation conditions will aid in advancing this technique to perform its intended function with high efficacy.

Methodology: Retina (N=43 from 23 mice) extracted from WT C57/BL6 mice were stimulated with 40 μs biphasic pulse trains with stimulation durations of 40 ms for frequencies 0.5-10 kHz and amplitudes 10-300 A. Frequencies were presented linearly or randomised to assess the effect of frequency order and adaptation on the RGC response. Preferential activation was calculated by taking the normalised spike count difference of the respective populations.

Results: Our results suggest that ON cells are less sensitive to frequency order than the OFF cells. Specifically, the ON cells were 10-25 % more likely to fire than their OFF counterparts consistently at higher frequencies (6-10 kHz) and amplitudes (250-300 μA) irrespective of the frequency order. While OFF cells also maintained a preferential space across all conditions, the region of activation was less consistent across the varying conditions suggesting their sensitivity to the sequence order. Under continuous KES, we found that ON cells were less sensitive to frequency adaptation compared to the OFF cells indicated by their robust preferential regions across the three continuous phases. Interestingly, the similarity between the preferential regions in which the frequencies were presented with the same frequency order and within the same pulse train suggests that both ON and OFF RGCs were able to reliably recover the spiking patterns following intermittent stimulation. Finally, we found that dynamic waveforms consisting of optimised, modulating frequencies could preferentially control the spiking activities of the ON and OFF cells.

Conclusion: We found that our proposed stimulation approach is able to quantitatively control RGC subtypes using high-rate electrical stimulation for more practical stimulation conditions. Further extending this work to different stage of degenerate retina will allow translation of these results for clinical applications.

Acknowledgement: This research is supported by Australia-Germany joint research co-operation scheme (DAAD).

Biography: Madhuvanthi Muralidharan received her B.E and M.E in Biomedical Engineering from Flinders University, Australia. She is currently a Ph.D. candidate in the Graduate School of Biomedical Engineering at UNSW, Sydney. Her research focuses on developing novel electrical stimulation strategies that are capable of selectively activating different retinal pathways. Her studies address one of the key and important challenges in implantable bionics of being able to accurately control the activation of retinal cells to restore the physiological processes associated with healthy vision. Additionally, she is interested understanding the intrinsic properties shaping the response of retinal neurons to electrical stimulation.

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Electronic "Photoreceptors" Enable Prosthetic Vision with Acuity Matching the Natural Resolution in Rats

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Purpose: Localized stimulation of the inner retinal neurons for high-acuity prosthetic vision requires small pixels and minimal crosstalk from neighboring electrodes. Local return electrodes within each pixel limit the crosstalk, but they over-constrain the electric field, thus precluding the efficient stimulation with subretinal pixels under 50□m. We developed two approaches to enhance the field penetration depth and investigated the resulting stimulation thresholds and acuity in vivo.

Methods: 1.5 mm-wide arrays of monopolar photovoltaic pixels, 20 or 40□m in size, having a common return electrode, were produced with and without the 25□m-tall polymer walls surrounding each pixel. A reduction in crosstalk was achieved by spatiotemporal modulation of the pixel photoconductivity, allowing surrounding pixels to act as transient local returns. Following the subretinal implantation in RCS rats, the full-field stimulation threshold was measured with 10ms pulses of 880nm light at 2Hz, while acuity was measured using gratings alternating at 2Hz, under 4ms pulses at 64Hz. Natural grating acuity in WT rats was measured using white light, for comparison.

Results: The full-field stimulation threshold was 0.06mW/mm2, corresponding to a current density of about 0.09mA/mm2 on the active electrodes, independent of the pixel size and presence of the walls. This is nearly 30 times lower than that with flat bipolar pixels of 40□m size. Grating acuity with 40□m arrays matched the pixel size, but with 20□m pixels, it matched the natural acuity of about 27□m in healthy rats. Optical spatiotemporal modulation of the photodiode conductivity allows converting any subset of pixels into transient local returns, thereby providing field confinement for high resolution and enabling the field shaping to be customized for individual retinal thickness and distance from the implant.

Conclusions: Photovoltaic prostheses with nearly-vertical electric field in the retina yielded stimulation thresholds independent of the pixel size, and much lower than those with flat bipolar pixels. Presence of the vertical walls did not negatively affect the retinal excitability, paving the way to honeycomb implants with local returns. With 20□m pixels in rats, spatial resolution appears to be limited by the retinal network integration rather than by the pixel size. However, in humans, where the 20/20 vision corresponds to 5□m stripes on the retina, we hope that 20□m pixels will enable restoration of central vision in AMDP patients with acuity as high as 20/80.

Biography: Daniel Palanker is a Professor of Ophthalmology and Electrical Engineering at Stanford University. He received M.Sc. in Physics in 1984 from the State University of Armenia in Yerevan, and Ph.D. in Applied Physics in 1994 from the Hebrew University of Jerusalem, Israel.

Dr. Palanker studies interactions of electric field with biological cells and tissues, and develops optical and electronic technologies for diagnostic, therapeutic, surgical and prosthetic applications, primarily in ophthalmology. In the range of optical frequencies, his studies include laser-tissue interactions with applications to ocular therapy and surgery, and interferometric imaging of the neural signals. In the field of electro-neural interfaces, he is working on high-resolution photovoltaic retinal prosthesis for restoration of sight and other implants for electronic control of organs.

Several of his developments are in clinical practice world-wide: Pulsed Electron Avalanche Knife (PEAK PlasmaBlade), Patterned Scanning Laser Photocoagulator (PASCAL), Femtosecond Laser-assisted Cataract Surgery (Catalys), and Neural Stimulator for enhancement of the tear secretion (TrueTear). Photovoltaic retinal prosthesis for restoration of sight (PRIMA) is in clinical trials.

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U.S. Food and Drug Administration Device Update

Overview: The U.S. Food and Drug Administration is committed to expediting innovation of vision restoration bioelectric implants. In this presentation, we will provide updated perspectives regarding vision restoration device regulatory submissions, highlighting relevant FDA programs, common device-specific review issues, gaps in the regulatory space, external collaborations, and plans for continued discussion to support development of these devices.

Biography: Dr. Sandrian is a Senior Staff Fellow, Lead Reviewer and Biomedical Engineer for the Retinal and Diagnostics Devices Team, Division of Ophthalmic Devices, Office of Health Technology 1, Center for Devices and Radiological Health. She joined FDA in 2015 and her areas of interest include ophthalmic imaging, ophthalmic lasers, vision restoration devices, artificial intelligence/machine learning based medical devices, electromagnetic compatibility, and medical device cybersecurity. Dr. Sandrian is a member of the Digital Health Focal Point Group, Human Factors Engineering Focal Point Group, and Electromagnetic Compatibility Community of Practice at CDRH. She is a Technical Expert for the ISO Working Group Committee on Optics and Photonics for standardizing test methods for Ophthalmic Optics and Instruments, and is also helping to develop related FDA guidance for industry. Throughout the COVID-19 public health emergency, Dr. Sandrian participated in review of Emergency Use Authorizations (EUA) and has also assisted with the development of immediately in effect guidance documents related to the COVID-19 public health emergency.

Prior to joining FDA, Dr. Sandrian was an Assistant Professor of Ophthalmology and Bioengineering at the University of Pittsburgh. She earned her Ph.D. in Bioengineering from the University of Pittsburgh, with a concentration in Neural Engineering, and participated in the Center for the Neural Basis of Cognition Graduate Training Program at nearby Carnegie Mellon University. She was selected as a Whitaker International Postdoctoral Scholar and completed postdoctoral training at the Center for Medical Physics and Biomedical Engineering in the Medical University of Vienna (Vienna, Austria).

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Characterizing Electrical Response Properties of Retinal Ganglion Cells Using Gaussian Noise Stimulus

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Purpose: This study aimed to characterize electrical properties of wild-type and rd10 mouse retinal ganglion cells (RGC) using electrical Gaussian noise stimulation. The results may help find an alternative stimulation strategy for conventional pulsatile stimulation by which different ganglion cell types can be targeted preferentially.

Method: A wide range of visual stimuli including full field flash, chirp, color, and moving bars were employed to assess the extracellular activity of RGCs recorded from 22 wild type and four rd10 retina using a standard 60 channel multi-electrode array (MEA). In the first step, a non-parametric clustering framework based on spike time distance metrics was implemented to cluster the light-induced activity of RGCs for healthy and degenerated retina. Additionally, Spike Triggered Averages (STA) of electrical noise-induced activity of clustered cells were computed and averaged for each cluster. In the second step, clustering was performed based on estimated STAs, and the average of light-induced activity was computed for each cluster.

Results: In line with previous studies, we found meaningful differences between the electrical input filters of two major ON and OFF cell types: hierarchical clustering of wild-type and rd10 retina light-induced activity yielded respectively 37 and 12 clusters. In wild-type retina, 4/7 of ON clusters reflected STAs with upward deflections whereas all 7 OFF clusters had STAs with downward deflection. Also, hierarchical clustering of STAs recognized respectively 15 and 23 different linear filter shapes for wild-type and rd10 data. Notably, Clusters with upward STAs were constructed only by ON cells, whereas clusters with downward STA reflected the activity of either OFF or ON/OFF cells (Figure 1).

Pharmacological block of photoreceptor-On bipolar cell synaptic connections in rd10 retina disrupted STAs with downward deflection but not STAs with upward deflection.

Additionally, we observed that 5 Hz rhythmic oscillations of rd10 STAs were abolished after application of blocker.

Conclusion: Application of linear system analysis and machine learning provided detailed information about the electrical characteristics of different ganglion cell types. Our results confirm previous reports stating that ON and OFF RGCs reflect different electrical input filters. Moreover, pharmacological manipulation of retinal circuits gave us new insights on neural mechanism of channel activation during subthreshold noise stimulation.

Biography: Hamed Shabani is currently a Ph.D. student at the Institute for Ophthalmic Research at the University of Tuebingen. He earned a B.S. degree in Electrical Engineering from Bahonar Technical College of Shiraz and an M.S. degree in Biomedical Engineering from Shahed University of Tehran, where he worked on developing a novel algorithm to detect drowsiness using EEG data. After completing his master's degree, he joined IPM as a research assistant, where he mainly worked on response variability in the visual cortex of nonhuman primates. In 2017, he moved to Germany to start his Ph.D. in Prof. Zrenner's lab under the supervision of Dr. Rathbun. For his doctoral project, he implemented an electrical noise stimulus to evaluate the response properties of retina ganglion cells during electrical stimulation.

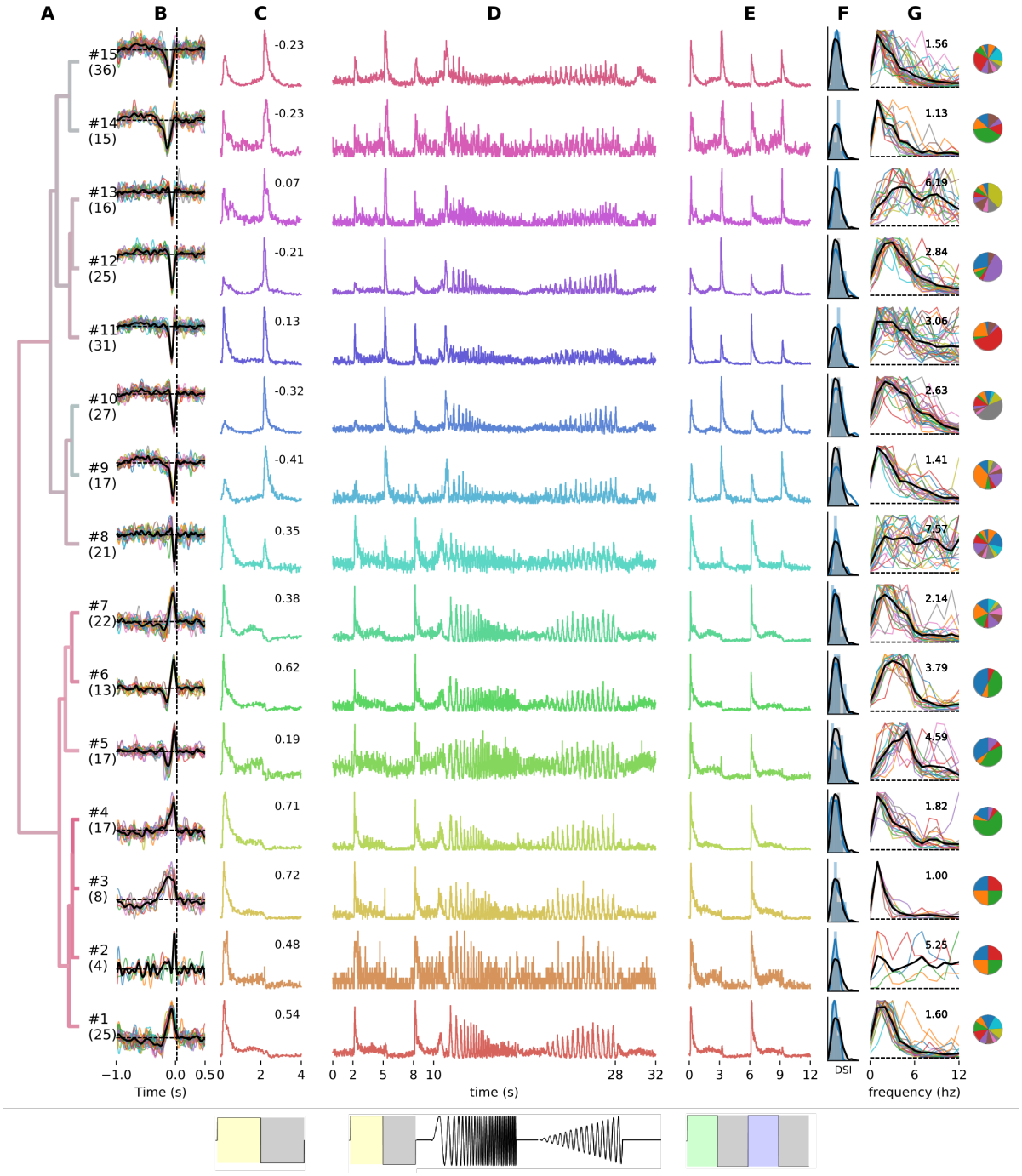
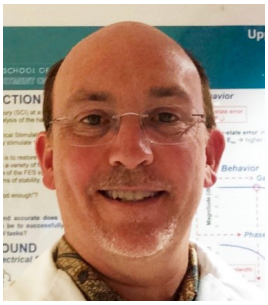


Figure 1. Hierarchical clustering of electrical input filters of wild-type retina shows correspondence between visual electrical profiles of RGCs. (A) cluster dendrogram shows two branches. (B) Clustered electrical input filters. First branch includes five clusters of STAs with positive peak. Second branch contains seven clusters of STAs with negative peak. (C, D, E) visual induced activity of Full field flash, chirp and color stimulus respectively. The numbers at plot (C) represents the ON-OFF bias index of each cluster. All cells in the first branch (clusters 1-7) respond only to stimulus onset. While, in the second branch (clusters 8-15) the light-evoked responses reflect the sensitivity to stimulus offset. Some of them have ON-OFF preference and some of them only OFF preference. (F) distribution of direction selectivity index. (G) Power spectrum of individual STAs(colored) and the average of Power spectrum of STAs for each cluster (black). Pie charts show the proportion of the neurons of each recording. Each color represents one retina.



Douglas Bourne Shire, Ph.D.
Bionic Eye Technologies
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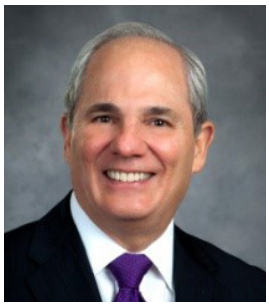

Joseph R. Rizzo, M.D.
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Microfabrication and Biocompatibility of Subretinal Electrode Arrays

Joseph F. Rizzo, MD, Massachusetts Eye and Ear Infirmary, Douglas Shire, Ph.D. and Marcus Gingerich, Ph.D., Bionic Eye Technologies, Inc., Jinghua Chen, MD, University of Florida, and Wei Wang, MD, University of Louisville

Objective: This work is related to the efforts of the Bionic Eye team to develop a visual prosthesis to restore basic vision following photoreceptor degeneration. A wirelessly controlled, subretinal device is being developed that incorporates arrays of >256 individually addressable stimulation electrodes that can also serve as local returns for current steering. We are validating these designs by testing the device, both in vitro and in mini-pig models.

Methods: We are advancing microfabrication methods over several device iterations to produce 256 channel, subretinally implantable electrode arrays that were bonded to our existing, miniature neurostimulator module. In addition, we adapt the associated RF coil and other implantable components to fit within the eye orbit under and between the rectus muscles. An external controller for the visual prosthesis has been redesigned, and its user interface software was updated to implement preclinical testing protocols. Meanwhile, our team addressed issues of hermeticity shifts in our packaging upon brazing the co-fired ceramic signal feedthroughs to the titanium packages. As well, the robustness of telemetry to and from our stimulator ASIC chip is improved through the use of a field programmable gate array (FPGA) based transceiver, and micro-fabrication methods creating hybrid penetrating - planar electrode arrays for the sub-retinal space were developed and will be presented.

Results: A custom surgical insertion tool is being used to help deliver silicon carbide-encapsulated flexible electrodes to the target tissue. In vitro testing of electrode arrays and coated test substrates at 87C will be presented, showing projected lifetime of >10 years. We improved the wireless transmission system for our device, which is now capable of full-duplex operation in addition to on-board monitoring of inter-pulse potentials on electrodes for device safety. Meanwhile, sub-retinal penetrating-planar combination arrays having 50-micron diameter electrodes located on the sub-retinal surface, on penetrating posts 50 microns deep within the retina, and on penetrating posts that are 100 microns deep within the retina, were fabricated. Our studies show excellent integration of such penetrating structures within the retinal tissue, with minimal glial tissue growth.

Conclusions: By employing electrodes of different types and amounts of penetration depth and optimizing aspects of our high density implantable neuroprosthesis designs and fabrication methods, we expect to be able to address multiple layers of retina tissue, resulting in high quality phosphenes that are individually controllable, and which have excellent integration with the target tissue.

Biography: Dr. Doug Shire is the President and CTO of Bionic Eye Technologies, Inc., and the longtime Engineering Manager of the Boston Retinal Implant Project, founded by Dr. Joseph Rizzo and the late Dr. John Wyatt in the 1980s. That Project's mission has been to develop visual prostheses and related technology to aid the visually impaired, and Bionic Eye Technologies was formed to commercialize those technologies. Dr. Shire has published extensively on the applications of microfabrication technology to medical device manufacturing, with special emphasis on implantable electrodes.

Biography: Dr. Rizzo is Board-Certified Neurologist and Ophthalmologist who has worked at the Massachusetts Eye and Ear Infirmary as a Neuro-Ophthalmologist since 1985. Since 2006, Dr. Rizzo has served as Director of the Harvard-wide program in Neuro-Ophthalmology. Dr. Rizzo dedicates his research to studying the mechanisms of vision loss, improving diagnostic methods, and developing new treatments for blinding diseases. Dr. Rizzo divides his time evenly between evaluating patients with Neuro-Ophthalmic disorders and performing research to better understand causes of blindness and to search for treatments to restore vision to the blind. In the late 1980s, Dr. Rizzo co-founded the Boston Retinal Implant Project as a multi-disciplinary research project based at Harvard Medical School and the Massachusetts Eye and Ear Infirmary with the goal of developing a retinal prosthesis to restore vision to patients with outer retinal degenerations. More recently, in collaboration with neuroscientists and neurosurgeons at Harvard's Massachusetts General Hospital, he has been leveraging the retinal technology to develop a visual prosthesis that interfaces with the brain at the level of the lateral geniculate nucleus, which potentially could treat blindness caused by inner retinal and optic nerve disease. His clinical research focuses primarily on the study of optic neuritis/multiple sclerosis, ischemic optic neuropathy, pseudo-tumor cerebri, and giant cell arteritis. Dr. Rizzo has founded two companies: Bionic Eye Technologies, Inc, which is pursuing development of the retinal prosthesis, and Visus, Inc, which has developed a suite of portable "apps" for Android phones sold through Verizon to assist the visually impaired.

Leili Soo, Ph.D.
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Assessing Visual Acuity in Low and Ultra Low Vision using Steady-State Visual Evoked Potentials

Leili Soo, Fabrizio Grani, Dorota Waclawczyk and Eduardo Fernandez

Purpose: Traditional visual acuity assessment tools are designed to measure visual function in normal vision using subjective reports. However, these tests lack sensitivity to measure meaningful variability in low and ultra-low vision which is essential both when evaluating clinical intervention effectiveness and when assessing whether and how much residual visual input is interacting with input provided by a visual prosthesis. Recently, an objective, non-invasive electroencephalography (EEG)-based method using steady-state visual evoked potentials (SSVEP's) was validated in normal vision (Zheng et al, 2020). Here, we present the parameters for an extension of this assessment tool for the use in low and ultra-low vision.

Method: We tested subjective visual acuity either by Freiburg Visual Acuity Test or by assigning low vision categories with approximate LogMAR values in 15 persons with visual disabilities. For the objective measurement, we collected EEG signals while participants viewed vertical sinusoidal gratings at different spatial frequencies corresponding to the sizes of the optotype in the Visual Acuity Chart (LogMAR units). To elicit SSVEP's, gratings were reversing pattern at 7.5 Hz. We used Fourier transform to calculate the SSVEP amplitude elicited by each of the spatial frequency condition. We estimated the acuity threshold as the smallest spatial frequency at which the SSVEP response was significantly bigger than noise level.

Results: We found that the amplitude of the grating-elicited SSVEP is reduced as the spatial frequency of the sinusoidal grating increases. We compared the acuity measurement result based on subjective and objective testing, finding a general agreement but an increased precision for the SSVEP- based tool.

Conclusion: We confirm that the SSVEP-based visual acuity assessment tool is suitable for the evaluation of visual acuity in low and ultra-low vision and provide a set of parameters and procedures to conduct this assessment. This tool allows for the direct quantification of the amount of visual information that reaches the occipital cortex without relying on non-precise low vision categorization or subjective reports.

References: Zheng, X., Xu, G., Wu, Y., Wang, Y., Du, C., Wu, Y., ... & Han, C. (2020). Comparison of the performance of six stimulus paradigms in visual acuity assessment based on steady-state visual evoked potentials. Documenta Ophthalmologica, 141, 237-251.

Biography: Dr Leili Soo is a Postdoctoral Researcher in a team lead by Professor Eduardo Fernández in the Neuroengineering and Neuroprosthesis Unit at the University Miguel Hernández in Spain. She received her Ph.D. in Psychology (Science) at the University of Aberdeen in Scotland. Her doctoral research focused on investigating the behavioural and neural mechanisms of visual crowding, a phenomenon in which object recognition is hindered in clutter. Currently, she uses behavioural and electrophysiological research methods to test ultra-low vision and blind human volunteers pre-, during, and post-intervention to assess the functioning of the neural prosthetic device based on Utah Electrode Array. Her work is a part of Horizon 2020 project NeuraViPeR (Neural active Visual Prosthetics for Restoring function), aimed at restoring vision using electrical stimulation of the brain.

Martin Spencer, Ph.D.
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Methods for Neural Activity Shaping in the Presence of Electrode Crosstalk

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Purpose: Existing bionic eyes have provided limited visual acuity even with increases in the number of electrodes (Edwards et al., 2018). This is due to crosstalk between electrodes, which leads to visual blurring (Wilke et al., 2011). This is due to the electrodes generating overlapping areas of neural activation. We have previously presented a method for simultaneous stimulation: The Neural Activity Shaping (NAS) strategy (Spencer et al., 2019). This method is based on an experimentally verified, linear-non-linear model of electrical stimulation (Maturana et al., 2016).

Methods: Four different extensions to the NAS strategy were investigated.

1. The effect of the choice of maximum safe electrode amplitude on the visual acuity under the NAS strategy was examined.
2. The effect of limiting the total power used was tested by including power in the objective function.
3. The visual field was expanded by manipulating neural activity beyond the spatial extent of the electrode array.
4. The potential to use opposite polarity pulse currents to induce neural activity to produce pronounced lines of low neural activity was investigated.

Each of the methods was explored in a computational simulation of neural activation.

Conclusion: We have shown that there are extensions to the NAS strategy that may increase its utility in improving visual acuity in circumstances with high levels of electrode crosstalk.

Biography: Martin Spencer is a research fellow in the Department of Biomedical Engineering, at the University of Melbourne, Australia with expertise in electrical stimulation strategies in retinal implants and computational models of the auditory brainstem. Martin completed a B.Sc. at Monash University in Melbourne, Australia with majors in physics and mathematics. In 2004 he completed an honours research project in theoretical physics. From 2005 to 2008 he worked as an accelerator physicist commissioning the particle accelerators at the Australian Synchrotron.

From 2009 to 2012 he undertook a Ph.D. at the University of Melbourne in computational neuroscience using spiking models of neurons to understand certain functions of the auditory brainstem. He continued work in this area as a research fellow at the École Normale Supérieure in Paris, the Institut de la Vision in Paris and the University of Southampton in the UK. Since 2016 Martin has been a research fellow in the Department of Biomedical Engineering in at the University of Melbourne. He currently works in collaboration with the company Bionic Vision Technologies on 'activity shaping' strategies to improve the resolution of retinal implants.

References: Edwards TL, Cottriall CL, Xue K, Simunovic MP, Ramsden JD, Zrenner E, et al. (2018) Assessment of the Electronic Retinal Implant Alpha AMS in Restoring Vision to Blind Patients with End-Stage Retinitis Pigmentosa, Ophthalmology, 125(3):432–443.
Maturana MI, Apollo NV, Hadjinicolaou AE, Garrett DJ, Cloherty S. Kameneva T, Grayden DB, Ibbotson MR, Meffin H (2016) A simple and accurate model to predict responses to multi- electrode stimulation in the retina, PLoS Comput. Biol., 12(4): e1004849. .
Spencer MJ, Kameneva T, Grayden DB, Meffin H, Burkitt AN (2019) Global activity shaping strategies for a retinal implant. J Neural Eng. 16(2):026008.
Wilke RGH, Moghadam GK, Lovell NH, Suaning GJ, Dokos S (2011) Electric crosstalk impairs spatial resolution of multi-electrode arrays in retinal implants. J. Neural Eng. 8(4):046016.

Results:

1. Limiting the maximum electrode setting limited the push-pull capacity of neighboring electrodes. This reduced the visual acuity when compared to the theoretical maximum levels. However, the visual acuity remained significantly higher than that created by the conventional sequential stimulation strategy (Figure 1).

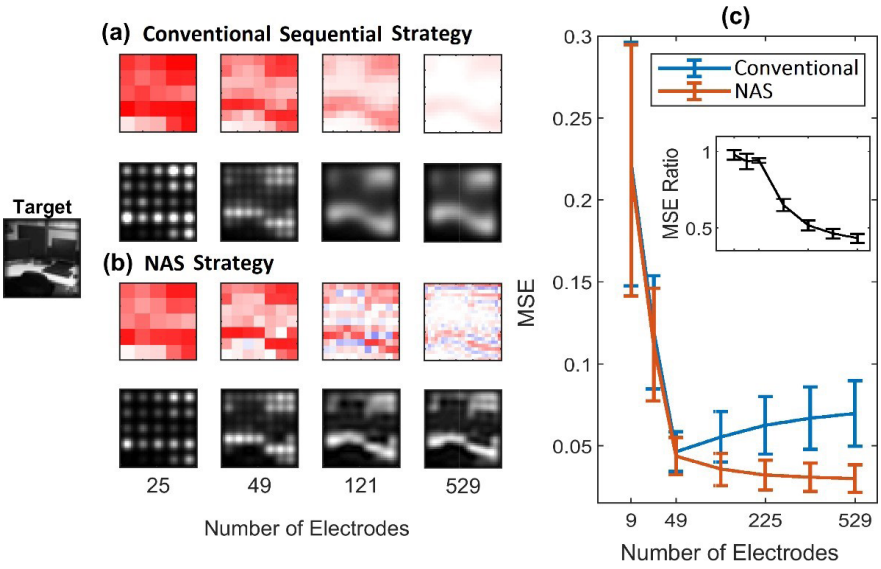

Figure 1: The effect of the maximum safe electrode amplitude (Method 1). a) and b) The electrode amplitudes and retinal activity using fixed electrode spreads (visible in the left-most column). c) The mean squared error (MSE) across 32 images.

2. A second benefit of explicitly controlling the power used by the method was control over the susceptibility of the method to noise.
3. It was found that the visual field could be expanded to render parts on the image outside the region bounded by the array. This was limited by the spread of neural activity induced by the electrodes.
4. The selection of opposite polarity electrodes led to improvements in image contrast.

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Light-Intensity-Controlled Stimulation of Neurons by an Organic Photovoltaic Interface

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Purpose: The non-genetic route to control the neural activity in retinal prosthesis requires a transient implantable device that can be activated either electrically or optically. However, optical stimulation is preferred over electrical stimulation because of its non-invasive process without any need for an external power supply and complex integrated electronics. High-efficiency transduction of light to bioelectricity is an essential goal for the realization of superior neuron-device interfacing.

Method: In this study, a single-junction, wireless, and capacitive-charge-injecting optoelectronic photoelectrode is designed and demonstrated by using bulk nano-heterojunction of PTB7-Th:PC71BM photoactive material. To investigate the membrane potential variation and generation of the action potential, in vitro experiments were carried on primary hippocampal neurons extracted from decapitated E15–E17 Wistar Albino rats using a patch-clamp rig.

Results: The logarithmic dependence of electrode-electrolyte interfacial photovoltage (Vph) and open-circuit voltage (Voc) of the photovoltaic device on incident light intensity was observed, which confirms the direct relationship between them. The peak capacitive photocurrent density was observed to be 511 A cm-2 with a negligible faradaic contribution. Moreover, we observed that while the light intensity increases, it leads to a faster switching of capacitive stimuli with our photoelectrode. The action potential was evoked when a burst waveform (1 ms on-time and 0.1 ms off-time) was applied, which has been demonstrated by Fromherz et al. by using electrical stimulation. This is the first demonstration of using burst light pulses with a high-Voc organic photoelectrode for capacitive photostimulation that results in action potential generation at low light intensity levels.

Conclusion: A high-Voc photoelectrode can lead to strong and fast capacitive currents at the electrode–cell interfaces. In addition, light can also control the switching speed of capacitive currents that are caused by the variation of Voc. Hence, the open-circuit voltage is an important design parameter for fast and effective switching of the neurons that can be controlled by light and electronic energy levels of the nano-heterojunctions. Also, some of the visual attributes can only be perceived at the threshold for the specific light pulses (in the sub-s region) and train frequency. Hence, the high-Voc photoelectrode can satisfy these crucial aspects as well. Therefore, bulk heterojunction composite-based photoelectrodes have a high potential for safe, rapid, and controlled neural photostimulation of cells. The proposed material has strong potential to be printed as a microelectrode array using a material printer for Bionic Vision.

Biography: Shashi B. Srivastava received B.S. and M.S. degrees in physics from Allahabad University and Banaras Hindu University, a M.S. degree in energy engineering from the Indian Institute of Technology Delhi. He pursued a doctorate in physics from Shiv Nadar University focusing on interface physics with an emphasis on optoelectronic properties of organic solar devices. He spent half a decade as a senior research associate and technical manager at Moser Baer India Limited in the Solar Photovoltaic Division. Immediately after graduation, he continued as a senior research fellow in Shiv Nadar University for the development of transparent polymer solar cells in a project from Department of Science and Technology, Government of India. In the beginning of 2018, he joined as principal researcher at KOC University in Istanbul, Turkey. There, he was part of a major European project researching optoelectronic devices for neural prostheses. Most recently, He has moved to the United States to research electrical stimulation of the retina. He is working on patch clamp recordings from the visual system as well as electrical stimulation of the retina for the restoration of sight.

He was awarded with prestigious GATE fellowship by Indian Institute of Technology. His scientific artwork was selected in the top 50 at a science art competition organized by Materials Research Society, USA. He has published over 25 research articles in major peer-reviewed scientific journals and conferences, and he is currently holding three patents. His current scientific research interests include bio photonics, optoelectronics, organic electronics, and nano photonics.

Conflicts of interest: There are no conflicts to declare.

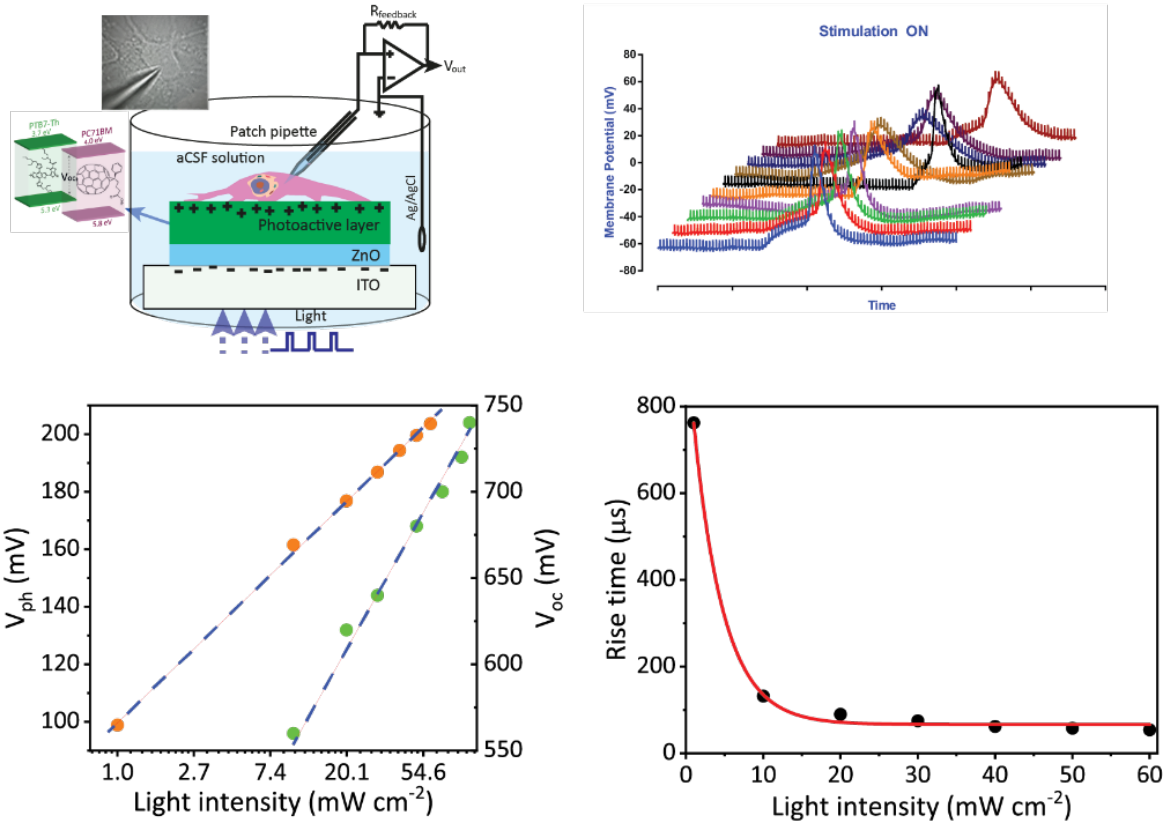

Figure: (a) Photoelectrode and a patch-clamp set-up schematic, (b) Membrane potential under light-pulse for single cell, (c) light-controlled variation of photovoltage and open-circuit voltage, and (d) light-controlled switching speed.

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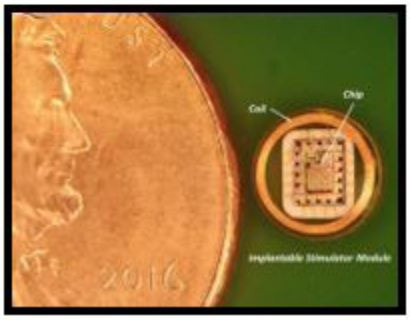
Chicago, Ilinois

INTRACORTICAL VISUAL PROSTHESIS (ICVP): FIRST PHASE OF THE CLINICAL TRIAL

PHILIP R. TROYK, Ph.D., Department of Biomedical Engineering, Illinois Institute of Technology

Purpose: Funded under the BRAIN Initiative, the Illinois Institute of Technology (IIT) is completing the third year of a team-based five-year project for a clinical trial of the IntraCortical Visual Prosthesis (ICVP. Our team has researchers from eight institutions: Illinois Institute of Technology, Rush University Medical Center (RUMC), University of Texas, Dallas (UTD), Johns Hopkins University (JHU), MicroProbes for Life Science (MLS), Sigenics, Inc, the Chicago Lighthouse for People who are Blind or Visually Impaired (CLH), and University of Chicago (UC). Using intracortical electrical stimulation of the human occipital cortex, we are investigating how to establish a stable chronic artificial neural interface and use it for communicating image information to individuals with blindness.

Methods: The ICVP uses a novel 16-channel implantable stimulator module: the Wireless Floating Microelectrode Array (WFMA). Each WFMA has wireless power and communication. An ensemble of WFMAs form a multichannel cortical interface. Having obtained both FDA and IRB approval, we have entered the first phase of the 3-year clinical trial in which recruitment and clinical device preparation are priorities. Recruitment during the pandemic poses significant challenges, as does supply chain disruptions related to WFMA manufacturing and sterilization. Furthermore, unexpected issues related to IRB approval resulted in our project shifting its medical partner from University of Chicago to Rush University Medical Center.



Results: The shift to RUMC has provided notable benefits to the project in terms of clinical trial support. Recruitment has used virtual techniques through CLH rather than the planned in-person information sessions. In some respects, it has been easier for people with blindness to participate in the informational recruitment sessions because many visually impaired persons have readily embraced technology. However, some apprehension on the part of potential study participants due to fears about the pandemic have retarded the recruitment process. Our study has a requirement for the participant to have little to no light perception, and it can be challenging to identify suitable candidates with this vision restriction. Outreach for recruitment has been dramatically increased and we expect to identify some of the five study volunteers in the next couple of months in order to fulfil our goal of implanting three persons in the next project year. During this period of delayed recruitment, we have been upgrading our participant testing capabilities.

Conclusions: The ICVP technology is a unique brain interface which is finding many candidate applications for use not only in the brain, but in the spinal cord and peripheral nerves. With the easing of pandemic restrictions, we expect the project to find the needed volunteers for ICVP artificial vision assessment.

Biography: Dr. Troyk is a Professor in the Department of Biomedical Engineering, the Executive Director of the Pritzker Institute of Biomedical Science and Engineering, and Affiliated Professor in the Stuart School of Business, at IIT. His research interests are broad and include cortical and retinal visual prostheses, implantable neural interfaces, functional electrical stimulation systems, design of neural prostheses, bioelectronic medicine, smart sensors, Radio Frequency Identification, telemetry, VLSI design, and packaging of implantable electronic devices. He obtained his B.S. in Electrical Engineering from the University of Illinois, Urbana, and the M.S. and Ph.D. in Bioengineering from the University of Illinois, Chicago.

Ieva Vebraite, M.Sc.
Tel Aviv University
Tel Aviv, Israel

Soft Organic Neural Interface for Recording and Stimulating the Intact Retina

Ieva Vėbraitėl, Moshe David Purl, David Randl, Eric D. Głowacki3 and Yael Haneinl,2
1 School of Electrical Engineering, 2 Sagol School of Neuroscience, Tel Aviv University, Tel Aviv 699780, Israel, 3 Central European Institute of Technology, Brno University of Technology, Purkyňova 123, 61200 Brno, Czech Republic

Purpose: Understanding the manner by which the retina converts a natural image or electrically stimulated one into neural firing patterns is the focus of on-going research activity. Ex-vivo, the retina can be readily investigated using multi electrode arrays. However, multi electrode array recording and stimulation from an intact retina has been so far scant. Realization of soft electrode arrays suitable for recording and stimulating neural activity in an intact retina is the purpose of the study.

Method: Screen-printing of carbon ink on 20 □m polyurethane (PU) film was used to realize electrode arrays with electrode as small as 40 □m in diameter. Passivation was achieved with a holey membrane realized using laser drilling in a thin (50 □m) PU film. Plasma polymerized EDOT was used to coat the electrode array to improve its specific capacitance. Values as high as 1-2 mF/cm-2 were achieved. Chick retinas, embryonic day 13, both ex-vivo and in the eye were used. Retinal stimulation with light and recordings were performed simultaneously.

Results: A novel fabrication process based on printed carbon electrodes was developed. Ex-vivo electrical recording of retina activity with carbon electrodes is demonstrated. With the addition of 200 μm in diameter organic photo-capacitors, simultaneous photo-electrical stimulation and electrical recording was achieved. Finally, electrical activity recording of intact retina was achieved inside the eye. Both blue light sensitivity and spontaneous retina waves were recorded and their features were analyzed.

Conclusion: Owing to unique properties the electrodes we described they can be used to achieve neural interfacing in a manner that has not been achieved before. Foremost, we were able to demonstrate an ability to simultaneously record and opto-electrically stimulate a retina at high fidelity. This new electrode technology can open new frontiers in the study of neural tissue in-vivo.

Biography: Ieva Vėbraitė-Adereth is currently a Ph.D. candidate at the School of Electrical Engineering at Tel Aviv University, under the supervision of Prof. Yael Hanein. Her current research interests include novel materials for retinal tissue stimulation and recording as well as electrode to tissue adhesion. She finished her first degree in Molecular biology at Vilnius University, Lithuania. Ieva conducted her M.Sc. research on improving recording and stimulating electrodes by silk and single protein 1 at Hebrew University (at the lab of Prof. Oded Shoseyov).

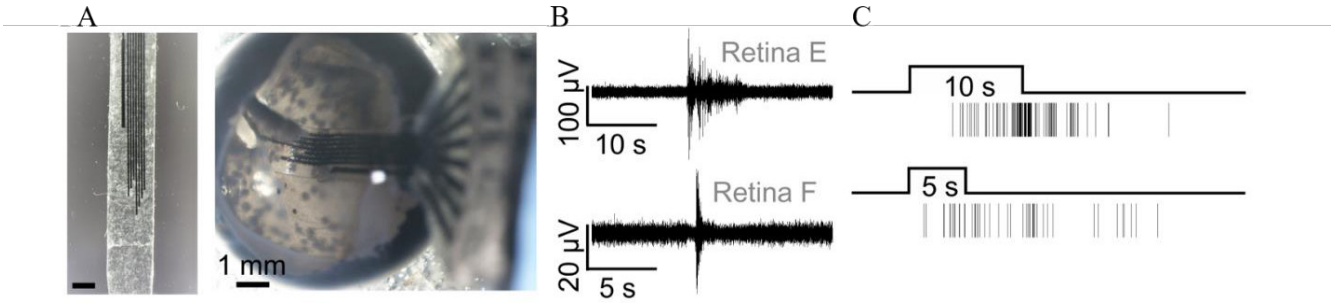


Figure 1. (A) SoftC probe (left), probe placed inside the eye (right). (B) Spontaneous retinal activity recorded in enucleated eye. (C) Evoked retinal spikes recorded in enucleated eye to 405 nm illumination.

Paul Werginz, Ph.D.
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Vienna, Austria

Morphological Features of RGCs and Their Influence on Threshold to Electric Stimulation

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Purpose: Indiscriminate activation of different types of retinal ganglion cells (RGCs) limits the quality of vision that can be achieved by implants. Cells of multiple types are confined to a small patch of the retinal surface which makes it hard to target each cell with a separate electrode. As a step towards more effective stimulation, a better understanding of 1) the influence of single anatomical properties of RGCs on thresholds, and 2) the morphological differences between different types of RGCs is needed.

Methods: The response of RGCs to extracellular electric stimulation was simulated using multi-compartment models. 40 model neurons were reconstructed based on anatomical and immunochemical data. The distribution of the electric potential was computed by analytical solutions for point source and disk electrodes.

Results: Electrode locations above the distal portion of the axon initial segment (AIS) resulted in the lowest threshold for all 40 model neurons. The exact location was dependent on the distance of the AIS from the soma as well as the AIS length. Dendritic diameter, soma diameter and AIS distance from the soma did not have an effect on thresholds, however, minimum threshold was negatively correlated to AIS length. This trend could still be observed when the stimulating electrode was positioned up to 100 µm from the model neuron. Passing axons from cells located distant to the stimulating electrode had thresholds approximately 2-5 times larger than AIS thresholds which was depended on AIS length, electrode type (point source vs. disk electrode) and electrode diameter.

Conclusions: Our computational study indicates that preferential activation across cell types is not likely to be achieved based on differences in AIS properties. Avoiding the activation of passing axons might be feasible by using microelectrodes located close to the ganglion cell layer. Additional testing using various pulse parameters can potentially facilitate focal stimulation.

Biography: Paul is currently an independent postdoctoral fellow at the Institute for Analysis and Scientific Computing at Vienna University of Technology and also holds a joint academic affiliation with Shelley Fried's lab at Massachusetts General Hospital / Harvard Medical School. He received his B.A., M.Sc. and Ph.D. from Vienna University of Technology in 2010, 2012 and 2016, respectively. Paul's research interests lie in the combination of computational and experimental neuroscience to improve the understanding of the mechanisms involved in the electrically stimulated retina – this knowledge will help to develop more sophisticated stimulating strategies for future retinal implants. Furthermore, he is interested in the anatomical and biophysical factors that shape the intrinsic properties of retinal ganglion cells.

Liancheng Yang, M.Sc.
Johns Hopkins University
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Variability in Relative Phosphene Mapping Techniques: Fine Tuning Local Clusters

Yang, Liancheng; Lee, Soo Hun; Sun, Helen; Dagnelie, Gislin

Purpose: When creating a phosphene map using absolute estimation techniques and using that map to present images to a cortical visual prosthesis wearer, there is an appreciable risk of distortions in the perceived image caused by errors in absolute phosphene locations. This problem is particularly vexing for phosphenes forming closely spaced clusters. In this study we sought to supplement absolute mapping techniques with relative ones, in order to disambiguate spatial relationships of phosphenes in such clusters.

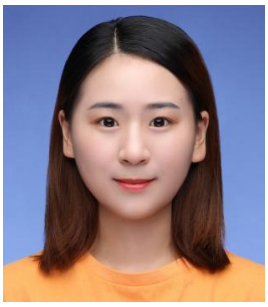
Method: Participants were seated at a table facing the center of a 36" diameter concave cap of a sphere with 24" radius, so their left index finger could comfortably reach the entire left half of the curved cap surface. A VIVE Pro Eye headset was used to record head and eye movements, and a Polhemus G4 tracker recorded the finger position. The center of the cap was marked by a bump dot to facilitate centering the finger while wearing the headset. At the start of each trial, the participant touched the center position while looking at a green dot shown in the headset, aligned with the tactile center dot. A pair of white dots, separated by 1° 8°, representing a phosphene pair within a cluster, was presented several times in alternation, and the subject was prompted to draw a line from the center of the cap representing the orientation of the imaginary line connecting the two phosphenes. By doing this for all closely spaced phosphene pairs in local clusters, local distortions can be reduced. A pilot study was carried out for 11 dot pairs randomly distributed at up to 35° in the lower 120°of the left hemifield and repeated three times in a session.

Results: To date, six participants with normal vision have been tested. Tracing directions for each dot pair were averaged within and then across subjects. Traced directions deviated from true directions by 9°±6° (mean±SD, across subjects) and were independent of dot separation; SD of the traced directions (within subjects) was inversely proportional with dot separation.

Conclusion: The small deviation angles demonstrated that a relative mapping approach limited to estimating relative directions only can be used as a reliable basis for rearranging phosphene pairs within local clusters. Limiting the paired setting to dots within clusters keeps the total number of pairs to be presented to a manageable number compared to the Nx(N1)/2 pairs required for a complete relative map. Combined with the absolute mapping techniques we are developing (presented elsewhere) this will allow a robust phosphene map construction within a reasonable time frame.

Biography: Liancheng Yang M.S., is a senior Program Analyst, System Manger at Ophthalmology in the John Hopkins University School of Medicine. He is from Tianjin, China. In 1983, he received his B.S. Degree in Application Physics/ Bio-Medical-Engineering, at NanKai University Tianjin, China. Then he worked as a clinical engineer at Tianjin Hospital for 13 years in Tianjin, China. In the meantime, he was sent to Japan to study MRI/MRS technology. In 1999, he received his M.S. degree in Computer Science from Towson University, Maryland US. After graduating, he started work in Cadmus Communications Corporation as a Software Developer.

Since 2001 he has been a team member of the Lions Vision Research and Rehabilitation Center (LVRRC), a division of the Wilmer Eye Institute at Johns Hopkins University, under supervision of Dr. Gislin Dagnelie, as a Sr. program analyst. During the past 20 years he has developed numerous software applications used in Dr. Dagnelie's research and managed the IT systems for multiple research projects in the LVRRC.



Zixin (Olivia) Ye, B.Eng.
City University of Hong Kong
Hong Kong, China

Responses of Visual Cortical Neurons to Aperiodic Electrical Stimulation of the Retina

Purpose: The sensory stimulations in nature are usually the aperiodic patterns, which often refer to a time-series signal that contains temporal noise, while the stimulation patterns commonly used in the laboratory are periodic. In vivo experiments were performed to compare the response of visual cortical neurons to periodic retinal electric stimulation with the aperiodic stimulus.

Method: We compared the cortical response to periodic with aperiodic retinal electrical stimulation in Sprague Dawley rats implanted a bipolar concentric stimulating electrode on epiretinal surface. A 2×3 grid electrode array was inserted into the primary visual cortex. Cathodic-first biphasic current pulses were delivered in 5, 10, and 20 Hz. The periodic train consisted of 20 constant inter-pulse intervals (IPIs). Rather, the aperiodic train consisted of mixed IPIs values that matched the mean IPI. There were four repetitions of each of the five possible IPIs in each aperiodic train. Three temporal noise levels, 10%, 30%, and 50%, were applied.

Result: Fig. 1 demonstrated the average spike rate for six rats in response to the periodic stimulation train with constant IPIs and the aperiodic train with random IPIs. This result showed that the aperiodic stimulation evoked larger responses than the periodic stimulus.

Biography: Zixin (Olivia) Ye is a Ph.D. candidate in the Department of Electrical Engineering at the City University of Hong Kong. She received her B.Eng. degree in Biomedical Engineering from Tianjin University in 2019. She conducts research in electrical retinal stimulation and electrophysiological recording of laboratory animals in Neural Interface Research Laboratory, advised by Dr. Leanne Chan. She is interested in bioelectrical signal processing.

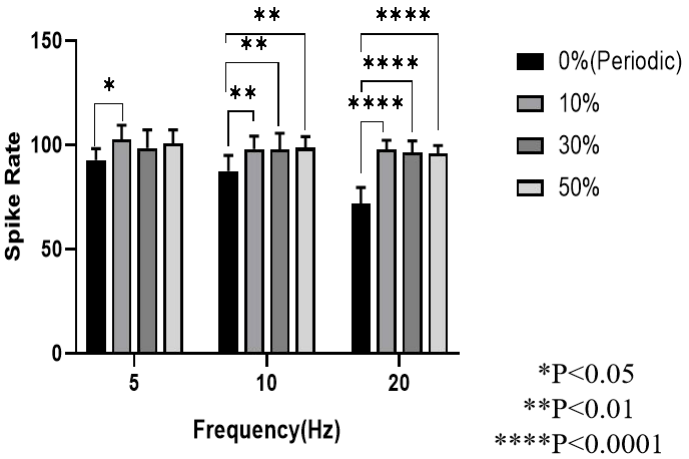


Fig. 1 Spike rate in response to periodic and aperiodic stimulation during the time window from the 1st stimulation onset to 50 ms after the final stimulation. Error bars represented standard error mean (S.E.M).

Fig. 2A-D showed raster plots and peristimulus time histograms (PSTH) of responses evoked by 10 Hz stimulation. The response to aperiodic stimulation (A,B) showed better temporal alignment to each individual stimulus than the periodic one (C,D). Fig. 2E illustrated the spike counts of different noise levels. It was found that the cortical response to the stimulation with higher noise levels showed less response decay, and maintained a higher response level throughout the stimulus train.

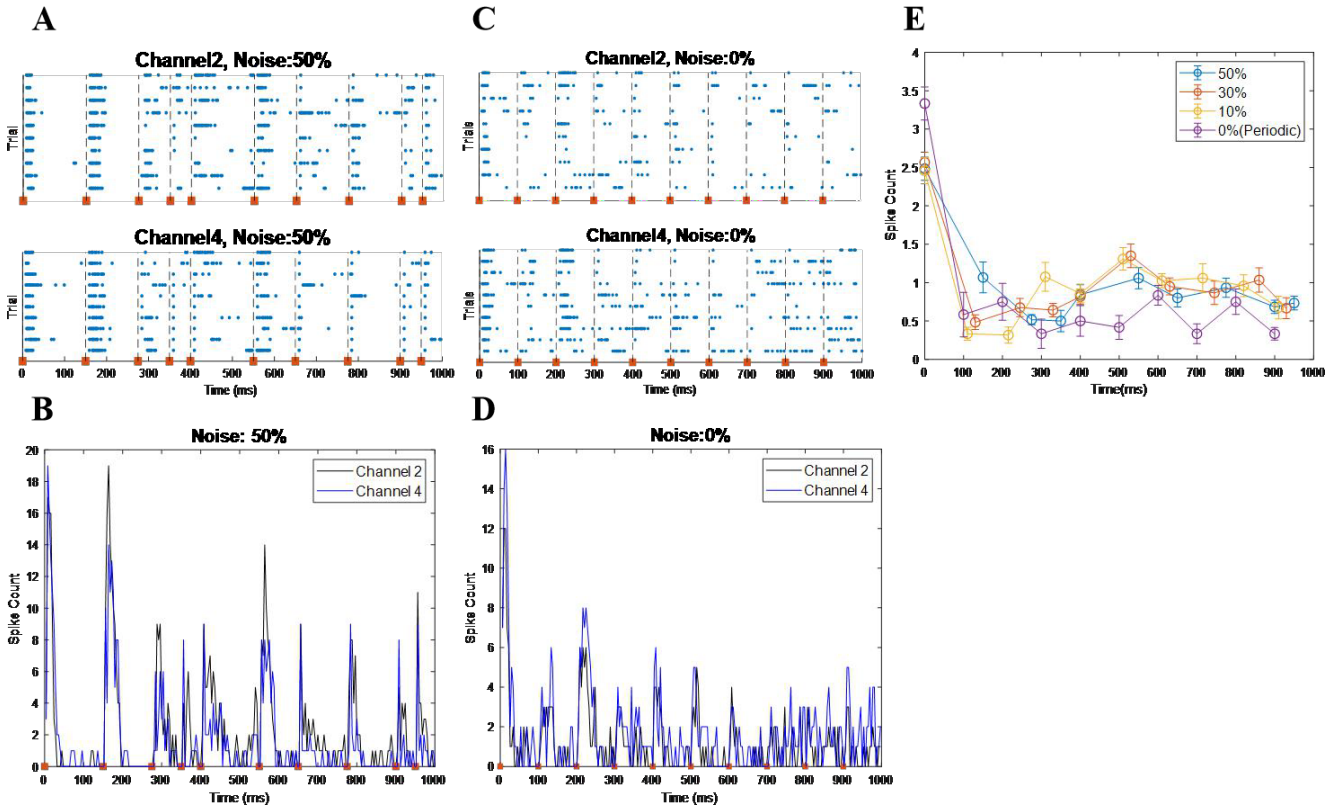


Fig. 2 Temporal precision of the response to the periodic and aperiodic electric stimulation.

Conclusion: When the electrical stimulations were applied to the rats' retina, at high frequencies (10 and 20 Hz), the aperiodic stimulation could evoke significantly larger responses than the periodic stimulus. The cortical response to the aperiodic stimulation had better time precision. Moreover, the aperiodic stimulation showed lower response decay with noise levels increasing.

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2021 World Congress:

The Eye and The Chip

POSTER PRESENTER ABSTRACTS

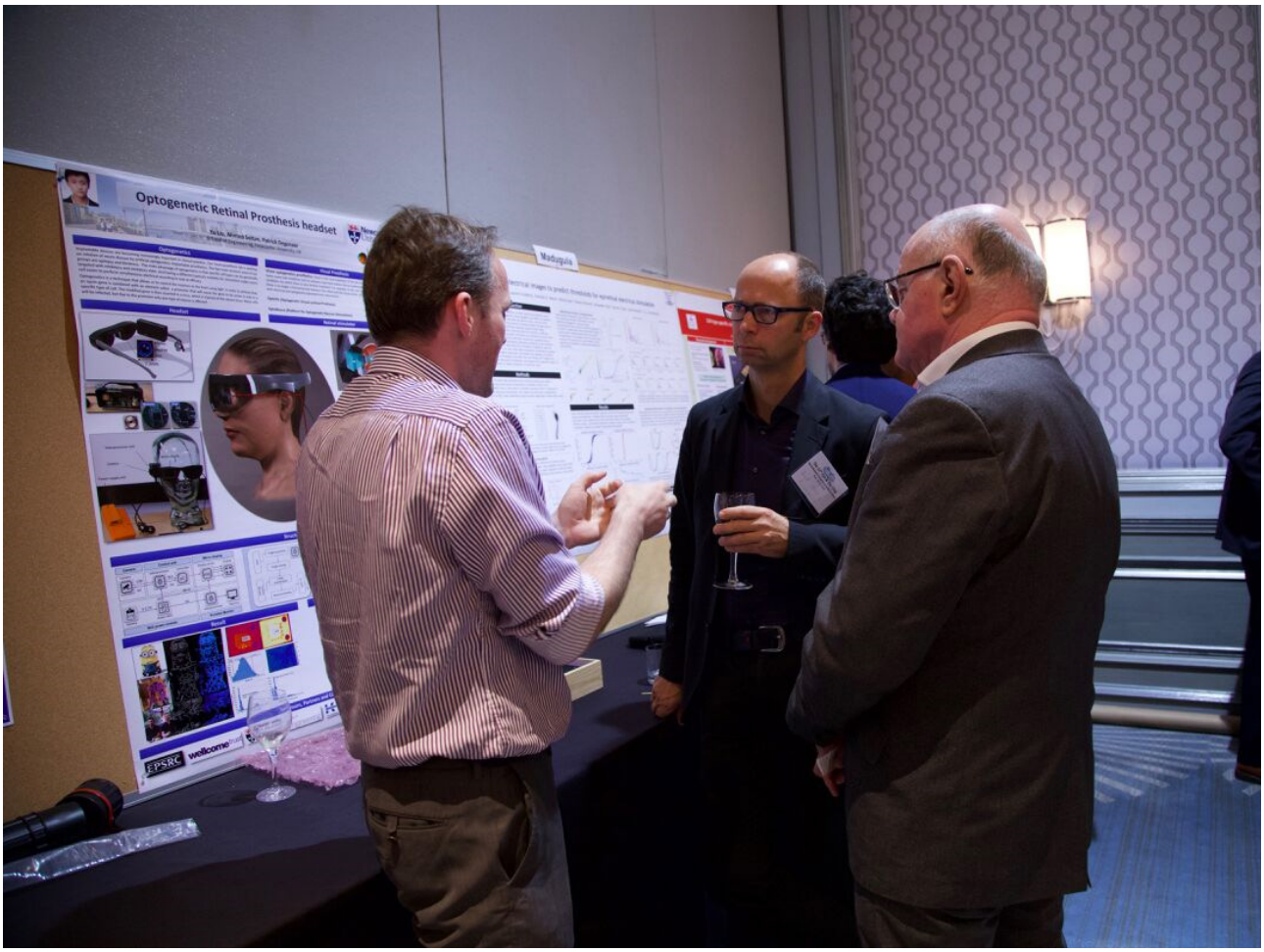

Photo from 2019 The Eye and The Chip Poster Session

DEPARTMENT OF OPHTHALMOLOGY

Detroit Institute of Ophthalmology

Thank You

William and Happy Rands

for your support of the
Poster Session

William C. Rands III
(1943 - 2021)

Dear Congress Attendees,

The Eye and the Chip lost a friend with the death of Bill Rands on June 20, 2021. For the past decade, Bill brought his keen intellect to our World Congresses as well as the financial underwriting of its poster sessions. Not much got past him. He was by no means a scientist, yet Bill attended every meeting, was fascinated by the presentations, and always asked penetrating questions.

Like countless others, we were lucky enough to call Bill a friend. But even those who knew him, saw only a few facets of this gem of man. A review of how he spent his time and energy gives a clear image of who Bill Rands was.

As an infant in East St. Louis, Illinois, Bill was adopted by William and Elizabeth Rands of Grosse Pointe who gave him the family stability and educational opportunity to succeed. After graduating from Yale with honors, he served as a lieutenant in the US Navy. Upon discharge he became what we now call an "investment banker" but his hugely successful business career was so creative and inventive that it defied a simple label.

Bill had the ability to see need that largely went unnoticed. Perhaps it was his own good luck--to be adopted out of poverty that fueled his empathy for those whose only luck was bad. His career gave him exposure to organizations dedicated to uplifting humanity. He lent his talent to directorial boards of various educational foundations, organizations dedicated to rescuing unfortunate victims--two-legged and four-legged--as well as conservation causes. Bill was an outspoken advocate for community health, serving on the board of the Henry Ford Health System. Himself a survivor of breast cancer, Bill unabashedly preached awareness for this uncommon but not rare condition in males.

If you knew Bill, you knew that he was a careful adventurer. He held a commercial pilot's license and loved nothing more than pointing his Beech Bonanza single-engine aircraft into the wild blue yonder. His other guilty pleasure was putting on his railroad engineer's cap and orchestrating the various model trains on the world-class layout in his basement.

Bill Rands' crowning achievement was his family. His 53-year marriage to Happy, also an adoptee, produced two children and four grandchildren.

The Eye and the Chip will miss Bill Rands. To commemorate his contributions to our World Congress, The Poster Session will be named for him.

Philip Hessburg, M.D.

Edward R. O'Malley, M.D.

Daniel Al Mouiee, M.Eng.
University New South Wales
Sydney, Australia

Deep Learning Techniques to Classify Retinal Degeneration in Histological Sections

Daniel Al Mouiee, Erik Meijering, Michael Kalloniatis, Lisa Nivison-Smith, Richard A Williams, David AX Nayagam, Thomas C Spencer, Chi D Luu, Ceara McGowan, Stephanie B Epp, and Mohit N Shivdasani

Purpose: Artificial intelligence techniques, in particular deep learning algorithms, are increasingly being used in ophthalmology to diagnose and predict the progression of ocular diseases from clinical images. Such techniques however have yet to be applied to histological data to classify the severity of retinal degeneration on a cellular level. In this study, we developed an automated deep learning algorithm capable of detecting the presence and classifying the severity of photoreceptor degeneration in standard retinal histological sections and compared its performance to a panel of experts in retinal disease.

Methods: Histological data for deep learning were based on a feline model of retinal degeneration. Briefly, four normal-sighted cats were injected with Adenosine triphosphate (ATP) and photoreceptor loss confirmed through electroretinography and optical coherence tomography. Up to 23 weeks post-ATP, animals were euthanized and eyes processed for histological analyses through Haematoxylin and Eosin stained retinal sections. Section images (n = 454) were split into training (n = 369 images) and testing (n = 85 images) sets. All images were graded by two assessors into four classes of degeneration (healthy, mild, moderate or severe) and used to train several convolutional neural network architectures. The testing set was evaluated through the best architecture and graded by an additional four assessors. Classifications by the algorithm and assessors were compared and inter-assessor variability was measured. Finally, the algorithm's robustness was tested by using less training images or images containing half the presentable context.

Results: The best architecture gave weighted-F1 scores in the range 85-90%, indicating its strong ability to predict the severity of retinal degeneration and identify images of healthy retina. Cohen kappa scores reached up to 0.86, indicating high agreement between the algorithm and assessors. Inter-assessor variability was consistent with the variability in the algorithm's ability to match predictions with the assessors. The algorithm was minimally affected by changing the training sets where reducing the training set size or image context resulted in a maximum reduction of 10% and 6% respectively, in the algorithm's performance.
Conclusions: Detecting the presence and severity of retinal degeneration in histological data can be reliably achieved using deep learning. This work lays the foundations for future deep learning algorithms which could aid in the evaluation of more intricate changes occurring in retinal degeneration and standardization of criteria used to evaluate retinal changes post photoreceptor loss.

Biography: Daniel Al Mouiee is a Radiotherapy Computer Scientist who currently works at the Ingham Institute for Applied Medical Research medical physics group (Sydney, Australia). His role involves developing tools to optimize various radiation therapy clinical processes for the Southwest Sydney Local Health District, as well as supporting/contributing to various medical physics research projects that involve data processing and deep learning. He graduated from the University of New South Wales, Sydney, with a Master of Biomedical Engineering and Bachelor of Software Engineering.

Changhoon Baek, Ph.D.
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Comparison of Optical Transparency and Hermeticity of Various Polymers for Retinal Prosthesis

Purpose: The purpose of this investigation is to search for an encapsulation material for a retinal prosthesis that can provide a longer working lifetime in vivo. Among the possible candidates, optical transparency was compared in preparation for protecting photodetector or photovoltaics which are utilized in some retinal implants.

Method: A custom phototransistor was fabricated on a silicon wafer and covered with various polymers. Only polymers were considered because they do not need designated feed through the neural electrodes. Polydimethylsiloxane (PDMS) and polyimide (PI) were chosen for their common use in the field. Colorless transparent polyimide (CPI) was added to the study for the possibility of replacing PI for optical benefits. Liquid crystal polymer (LCP) and cyclic olefin copolymers (COC) were added due to their high working lifetime expectancy.

Result: As expected, PDMS, CPI, and COC showed great optical performance compared to PI and LCP. From the independent t-test, the PDMS-COC pair showed $p > 0.05$, but COC-CPI pair showed $p < 0.05$. In terms of their characteristics, PDMS and CPI are thermoset polymers while COC is a thermoplastic polymer. Although most of the current state-of-the-art retinal implants are based on thermoset, these were found to be vulnerable to layer dehiscence. Contrarily, layers of thermoplastic can be fused when sufficient heat and pressure are applied.

Conclusion: From recent reports, LCP and COC both showed excellent results in the accelerated soak test, with an expected working lifetime of over five years in vivo. With excellent optical transparency, we believe COC is worth further investigation for hermetic encapsulation of retinal prosthesis.

Biography: Changhoon Baek received his BA.Sc. degree in electrical engineering from the University of British Columbia, Vancouver, Canada, and his Ph.D. degree in electrical engineering from Seoul National University, Seoul, Republic of Korea. He is currently a post-doctoral researcher in Bio-mimetic Robot Research Center, Seoul National University, Seoul, Republic of Korea. His research interests include implantable devices, neural prosthesis, and brain-machine interface.

Mohajeet B. Bhuckory, Ph.D.
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Characterization of Retinal Simulation and Integration with a Subretinal Honeycomb-shaped Prosthesis

Mohajeet B. Bhuckory, Zhijie Charles Chen, Bing-Yi Wang, Tiffany Huang, Ludwig Galambos, Andrew Shin, Theodore Kamins, and Daniel Palanker

Purpose: In patients with geographic atrophy, subretinal photovoltaic implants with 100 m pixels provided prosthetic acuity of 1.1-1.3 pixels (20/460 – 20/560). Rats with implants of 75 and 55 m pixels also demonstrated grating acuity matching the pixel pitch. However, stimulation threshold rapidly increases for smaller flat bipolar pixels and exceeds the safe charge injection limit with pixels below 40 m. To decrease the stimulation threshold and decouple it from the pixel width, we added vertical walls surrounding each pixel. This approach relies on migration of the retinal cells into these honeycomb-shaped wells. Here, we investigate the structural integration of the inner retinal cells with the wells and its effect on retinal response to stimulation.

Methods: To evaluate the effect of honeycombs on retinal stimulation threshold, 25 m tall walls were polymerized on flat photovoltaic arrays with 40 m and 20 m pixels. Visually evoked potentials (VEP) were recorded weekly after implantation and retinal anatomy was examined by confocal imaging of the immuno-labelled whole mounts.

Results: With both, flat and honeycomb implants, VEP amplitude decreased after the day of implantation and then gradually increased back to the original level during 6-9 weeks post-op. However, stimulation thresholds with honeycombs and flat implants of both pixel sizes remained the same: 0.057±0.029 mW/mm2. Majority of cells populating the wells were cone and rod bipolar cells, and much fewer horizontal cells. The macro- and micro-glial response to the honeycomb implants were comparable to that with flat implants and to the degenerate retina controls. The deep capillary plexus (DCP) and amacrine cells, as well as the inner plexiform layer remained entirely above the honeycomb walls.

Conclusions: Retinal migration into the honeycombs does not negatively affect its electrical excitability. Lack of cell death indicates that DCP above the wells provides oxygenation and nutrients to cells within the wells. Comparable glial response to flat implants suggests that migration and separation of the retinal cells by the walls in the INL does not cause additional stress. The 25 m deep wells accept majority of the INL, while leaving the tertiary neurons, such as amacrine and ganglion cells, outside. This is important for selective stimulation of the secondary neurons and preservation of the inner retinal signal processing in prosthetic vision.

Biography: Mohajeet Bhuckory, Ph.D., is an instructor in the Palanker lab at Stanford University. His work focuses on restoration of sight after photoreceptor degeneration. In addition to photovoltaic array implantation and testing in animal models, Dr. Bhuckory is interested in the interactions between retinal cells and the subretinal arrays.

Maya Carleton, B.Sc.
University of California, San Diego
San Diego, California

Electrical Stimulation Synchronizes Activity Over Space and Time in the Degenerating Retina

Purpose: The goal of retinal prosthetics is to restore vision by replacing the function of lost photoreceptors with optoelectronic hardware to sense light and interface with the remaining retina, thus restoring visual signals to the brain. One consideration to this strategy is that remodeling of the remaining retinal circuit occurs after photoreceptor loss, resulting in abnormal spontaneous activity. Much work has described the properties of this spontaneous activity, as well as the circuit and biophysical origins. However, less work has focused on how electrical stimulation interacts with the altered retinal circuits to modulate spontaneous disease mediated activity and alter the fidelity of evoked stimulation.

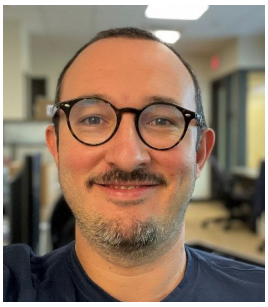
Methods: By comparing electrical stimulation evoked responses in RGCs of both wild-type and Rd10 mouse retina, we examined how retinal degeneration mediated remodeling alters the spread of both evoked and spontaneous activity over retinal area and through time. Custom stimulating arrays were fabricated to deliver current pulses and loose patch recordings were gathered from RGC's. Pharmacological manipulations were preformed to inhibit, excitatory, inhibitory, and gap junctional circuits in order to isolate the origins of oscillatory spontaneous activity.

Results: We found that electrical stimulation coordinated RGC activity over greater distances in rd mice, compared to wild type. Similarly, we found that electrical stimulation synchronizes oscillatory activity over longer timescales for rd compared to wilt-type retina. Importantly, the extent of this spatial and temporal coupling is dependent on the strength of electrical stimulation. In addition, pharmacological experiments implicate the AII-CBC gap junctional network level as the locus for abnormal coupling, rather than direct RGC coupling or outer retina networks.

Conclusion: Together our results demonstrate that spatial and temporal precision of electrical stimulation is negatively impacted in the rd retina, beyond simple degradation of the signal to noise. Our results showing stimulation strength dependent coupling indicates that there may be practical upper bounds to stimulation strength beyond the electrochemical properties of the electrodes or response saturation. These findings have important implications for the limits of the reproduction of complex spatial and temporal patterns of neural stimulation for retinal prosthetics, and strategies to achieve usable prosthetic vision.

Biography: Maya Carleton is a post-baccalaureate researcher in Dr. Nicholas Oesch's laboratory at the University of California, San Diego. After receiving her bachelor's degree in Cognitive and Behavioral Neuroscience from UCSD, she switched her research interest from primate cognitive neurophysiology and became interested in retinal degeneration and optical prosthetics. Her current research focuses on aberrant activity in the degenerating retina, and the circuit interactions with electrical stimulation, for mouse models of retinitis pigmentosa. She hopes to peruse her Ph.D. in Neuroscience in the coming years.

Conflict of Interest Statement: These studies were supported by a grant from NIH (EY029259 to NWO). Author NWO has an equity interest in Nanovision Biosciences, Inc. and also serve on the Scientific Advisory Board. Although this grant has been identified for conflict of interest management based on the overall scope of the project and its potential benefit to Nanovision Biosciences, Inc., the research findings included in this work may not necessarily relate to the interests of Nanovision Biosciences, Inc. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.



Mahmut Emin Celik, Ph.D.
Bioelectronic Vision Lab
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A Computational Model for Cortical Stimulation Comparing Realistic Electrode Geometry vs a Point Source

Mahmut Emin Celik, Kathleen E. Kish, and James Weiland

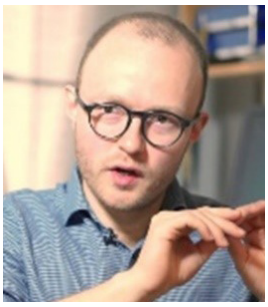
Purpose: The idea of a cortical visual prosthesis for vision restoration is based on visual perceptions which are created by electrical stimulation of the visual cortex. As a complementary method to experimental studies with surface and penetrating electrodes, computational modeling of cortical electrical stimulation has the potential to improve clinical outcomes by providing both accurate predictions and optimization of electrode design and stimulation parameters. This work aims to use computational modeling to study neuron responses to intracortical electrical stimulation. We compare modeling using a realistic electrode design vs. a point source and place the model neuron at various locations relative to the electrode/source.

Method: A multi-compartmental rat neocortical pyramidal neuron model with 3-D geometry was implemented in NEURON 8.0 simulation software. Biologically realistic membrane properties such as passive properties and Hodgkin–Huxley type voltage-gated channels were inserted to neuron compartments except myelinated axon. As a volume conductor model, a rat head model included four layers as scalp (10 mm), skull (9 mm), cerebrospinal fluid (8.5 mm) and brain (8 mm) with realistic electrical and physical values in COMSOL 5.5 [Moffitt et.al.]. Electrical stimulation was modeled from two sources: 1) a carbon fiber electrode with 70 um exposed length, 2 mm total length and diameter of 6.2 um tapering to a 2-um diameter tip and 2) a point source. The model neuron was placed in 7 different locations. Activation threshold was determined by applying a biphasic pulse with pulse width of 400 us and 20 Hz frequency for 250 ms simulation duration.

Results: Cortical electrical stimulation with a penetrating carbon fiber electrode and a point source were simulated. Additionally, action potential initiation point was also determined. It was shown that threshold currents for CF electrode and points source are 31uA-468uA and 39uA-504uA respectively, for seven different locations. Initiation points differ from axon, dendrite, and soma depending on the placement of the neuron with respect to the source.

Conclusion: It is seen that the activation threshold is strongly dependent on the distance between neuron and intracortical electrode. Axonal compartments are prone to fire action potentials preferentially compared to other compartments of the model. Computational neural models incorporated with electric field computations can be used to explore single cell stimulation characteristics and stimulation design parameters before experimental work. For the electrode shape and electrode-neuron distances tested, the point source and realistic electrode models threshold predictions agreed within 20%.

Biography: Dr. Celik received his Ph.D. in Electrical and Electronics Engineering at Gazi University, Ankara, Turkey, where he is now an Assistant Professor. In his PhD project, he focused on retinal ganglion cell responses to electrical stimulation. After a brief period in the Experimental Retinal Prosthetics Group, Institute for Ophthalmic Research, University of Tübingen funded by Erasmus+ and German Academic Exchange Service (DAAD), he worked as a visiting scholar in Retinal Information Processing Group, Intitut de la Vision, Paris between 2018 and 2019, then joined the Bioelectronic Vision Lab, Biomedical Engineering, University of Michigan as a Fulbright Visiting Scholar Fellow in 2021. His current work includes both analysis of extra striate cortex responses to various electrical and light stimulations and computational modeling to better understand factors for visual cortex stimulation design.



Rasmus Schmidt Davidsen, Ph.D.
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Interaction Between PC12 cells and 3D Carbon Pillar Electrodes for Subretinal, Photovoltaic Prosthesis

Rasmus Schmidt Davidsen, Alice Le Friec, Stephan Sylvest Keller, Toke Bek

Purpose: This work investigates physical interaction between cultured cells and carbon pillar electrodes intended for photovoltaic implants. Our hypothesis is that cells and tissue tend to adhere to 3D carbon pillars. If verified, this underlines the potential of such 3D carbon structures as suitable electrodes for retinal prosthesis.

Methods: Si implants were fabricated as in (1). The chip was sterilized with UV light then coated with 0.01% collagen IV before seeding of 4000 PC12 cells (passage 14) in growth medium. After 72h, the medium was changed to neural differentiation medium for 12 days. PC12 cells on the chip were fixed with 4% paraformaldehyde, dehydrated in graded series of ethanol baths and sputter coated with 6 nm platinum prior to scanning electron microscope (SEM) imaging. Polydopamine (PDA) was deposited by electrodeposition, polymerized and heat-treated at 200 . The PDA coating was then removed at the tip with a 355 nm, 25 W laser.

Results: Figure 1 (a,b) shows scanning electron micrographs of the PC12 cells deposited on the surface of the Si chip with pyrolytic carbon pillars. The cell nuclei seem to adhere to the tip of the pillars with axons extending from the nuclei and connecting neighbor cells each positioned on a carbon pillar. Figure 1 (c,d) shows how carbon pillars may be passivated by PDA, which is then selectively removed from the tip of each pillar by a laser.

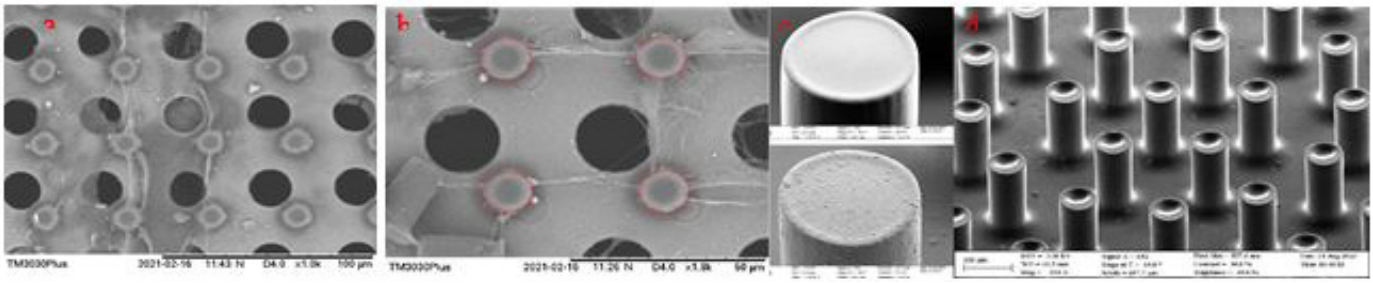

Figure 1: (a) PC12 cells on the surface of a photovoltaic Si chip with 3D carbon pillars. Cell nuclei are indicated by red circles (b) and seem to be placed at the very tip of the carbon pillars. 3D carbon pillars (c. top) with polydopamine (c, bottom) passivation and after removing the passivation layer at the tip of every carbon pillar using a laser (d).

Conclusion: PC12 cells adhere to tips of carbon pillar electrodes. Cell nuclei seem to be in contact with the carbon electrodes. This is encouraging for the potential of using such 3D carbon electrodes in retinal prosthesis. 3D carbon pillars were passivated by PDA and we show that the passivation can be selectively removed on the tip by using a laser. This result encourages better confinement of the electric field and output current from such electrodes, potentially leading to less cross-talk between neighbor electrodes and higher local current density for the individual pillar electrode.

Biography: Rasmus Schmidt Davidsen is a researcher at the Technical University of Denmark (DTU), Department of Micro- and Nanotechnology, working with photovoltaic retinal implants. Rasmus Schmidt Davidsen holds a Ph.D. in nanotechnology, which he completed in 2016 with a thesis focused on nanostructured silicon solar cells. Rasmus is still involved in the solar cell activities at DTU Nanotech, especially focused on 'black silicon'; a research area, which he has driven and been intensely involved in since 2010. His current research focuses on the development of a photovoltaic subretinal implant based on thin silicon combined with pyrolytic 3D carbon electrodes. The research project is a strong collaboration between Rasmus and the group of Professor, Med.Sc.D Toke Bek at Aarhus University Hospital. Rasmus is 35 years old, lives in Aarhus, Denmark, and holds a M.Sc., B.Sc. in materials science and nanotechnology from DTU. Throughout his studies, Rasmus has visited University of Illinois at Urbana-Champaign, USA, and University of New South Wales (UNSW), Sydney, Australia.

(1) Davidsen et al. "Evaluation of the capacitive behavior of 3D carbon electrodes for sub-retinal photovoltaic prosthesis", Micro and Nano Engineering 2, 110-116, 2019

Elena Della Valle, Ph.D.
University of Michigan
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Intraretinal Stimulation with Sharp Carbon Fiber Microelectrodes

Elena Della Valle, Dorsa Haji-Ghaffari, James Weiland

Purpose: Neural interfaces based on carbon fiber electrodes have demonstrated key positive attributes such as good neural recording, minimal foreign body response and mechanical strength to self-insert in brain tissue. In our work we use platinum iridium coated carbon fibers (PtIr-CF) to perform intraretinal stimulation and record retinal ganglion cell (RGC) spatial activity using calcium imaging.

Methods: Mice C57BL/6 (n = 3) were injected with pGP-AAV-CAG-jGCaMP7f-WPRE and retinas were harvested 3 – 4 weeks after injection. Animals were anesthetized with ketamine (100 mg kg-1) and xylazine (10 mg kg-1). Both eyes were enucleated and hemisected inside a perfusion chamber filled with bicarbonate-buffered Ames' Medium (Sigma-Aldrich, St. Louis, MO). Retina was mounted with retinal ganglion cells (RGC) facing down in the transparent chamber to allow for calcium imaging. CFs were inserted from the outer layer (photoreceptor side) of the retina and the tip was positioned 100 m below the insertion point. CF arrays consists of 16 sharpened carbon fibers (80 m pitch) with electrodeposited PtIr, each array Each 400 m carbon fiber was supported with a silicon shank (6 mm long). Parylene-C insulation layer (800 nm) covered the device. The carbon fiber tip is exposed (insulation removed) with a sharpening process (blowtorching) that resulted in 100-150 m length of carbon exposed (1700 m2 area). Platinum Iridium alloy was electrodeposited on the tips.

Results: We measured RGC activation thresholds for 10 regions across three retinas. The average threshold was 13 ± 7 A (average charge density of 0.37 ± 0.2 mC/cm2) with a distant ground wire placed in the bath. Lowest and highest thresholds were 5 A (0.17 mC/cm2) and 25 A (0.74 mC/cm2) respectively. The high standard deviation for thresholds might be due to variations in calcium expression in different regions. We measured thresholds with a local ground (the adjacent CF was used as ground) in three regions. Thresholds did not change with local ground in two regions and slightly increased in one region. Pulsing with two adjacent CF at the same time did not change the activation thresholds.

Conclusion: Here we used PtIr-CF to stimulate the retina and record RGC spatial activities. Intraretinal stimulation has the potential for high resolution activation of retinal cells.

Biography: Dr. Elena della Valle, received a Bachelor's degree in Clinical Engineering (2007 - 2011) and a Master's degree in Biomedical Engineering (2012 - 2014) from Sapienza, University of Rome, Italy. She is currently a research fellow at Bioelectronic Vision Lab at University of Michigan, Ann Arbor, USA. Her main research areas are: PtIr electroplating techniques, in vitro and in vivo neural recording and stimulation, microelectrode technology, computational modeling.

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Towards Calibrated Computer Models for the Optimization of Parallel Stimulation

Ariastity M. Pratiwi, Samuel C. Eggenberger and Gregg J.Suaning

Purpose: Electric crosstalk can impair the acuity of the restored vision during parallel stimulation of the retina from multiple sites. Hexapolar stimulation is effective in limiting crosstalk by returning the stimulating current through six guard electrodes arranged in a hexagon, but at the cost of higher thresholds. Many in vivo studies of retinal stimulation use an arbitrary definition of stimulation threshold as the current which causes 50% of the maximum firing rate (P50) at the visual cortex. While it is a useful indicator of stimulation efficacy, translating the P50 into a threshold for computational models is not trivial. Our study aims to develop a model with parameters that predict in vivo P50 thresholds to better understand parallel stimulation using varying combinations of hexapolar and monopolar currents.

Method: A Finite Element Method model with realistic retinal layers was built to measure the electric field distribution in the retina upon electrical stimulation. Threshold parameters, the electric field threshold (Eth) and the surface area of the ganglion cell layer above the Eth (Sth), were calibrated against the empirical hexapolar and monopolar P50 values from literature. The Sth was used to predict the P50 thresholds for combined monopolar and hexapolar stimuli delivered from a single electrode. The predictions for this quasimonopolar (QMP) paradigm, where part of the stimulating current is returned through the hexapolar returns and the remaining current is returned through a distant ground, were compared to the published in vivo data. The model was then generalized by gradually increasing the separation between the hexapolar and monopolar current sources.

Result: The Eth and Sth values can be used to predict the experimental QMP P50 thresholds when hexapolar and monopolar currents are delivered from a single location (Figure 1, Eth= 2463 V/m, Sth=766625 m2 ±2.8% at 95% CI). This model indicated that QMP reduces the P50 thresholds up to 1.5 mm electrode separation but did not predict the empirical P50 thresholds at 2 mm separation.

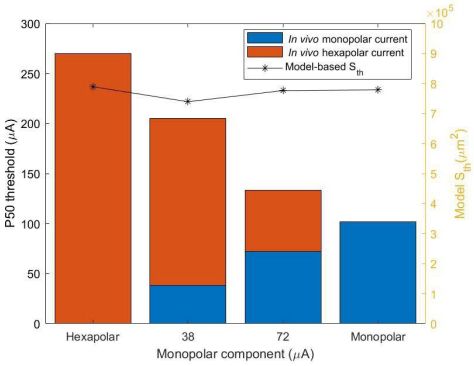

Figure 1: The predicted Sth values are consistent with the literature across different combinations of hexapolar and monopolar components.

Conclusion: The combined values of Eth and Sth form a predictor of the P50 when the stimulating electrodes are co-located. Further work is needed to generalize the computational model and quantify the effects of QMP during parallel stimulations from multiple sites.

Biography: Samuel Eggenberger is a Ph.D. student in the SydneyBIONICS Laboratory at Sydney University, Australia. He graduated from EPFL (Swiss Institute of Technology Lausanne) with a B.Sc. degree in Microengineering in 2010 and received the M.Sc. degree in Biomedical Engineering from ETHZ (Swiss Institute of Technology Zurich) in 2013. From 2014 to 2018, Samuel was an R&D Project Engineer at Stryker, developing comprehensive surgical platforms for the treatment of complex orthopedic cases. He returned to academia in 2018 to focus on prosthetic vision and means to evaluate the safety and efficacy of retinal implants to accelerate their journey towards clinical applications.

Rebecca Esquenazi, M.A.
University of Washington
Seattle, Washington

Learning to See Again: Perceptual Learning of Abnormal On-off-cell Population Responses Produced by Sight Recovery Technologies

Rebecca Esquenazi, Michael Beyeler, Geoffrey M. Boynton, & Ione Fine

Purpose: Many forms of artificial sight recovery, such as electronic implants and optogenetic proteins, cause unnatural simultaneous firing of on-and off-center retinal cells. Here, using 'virtual patients' – sighted individuals viewing input which mimics these distortions – we examine whether plasticity might compensate for abnormal neuronal population responses.

Method: Five participants were dichoptically presented with a combination of original and contrast-reversed images as a proxy for abnormal on and off-cell stimulation. Each image (I) and its contrast-reverse (I') was filtered using a radial checkerboard (F) and its inverse (F') in Fourier space. [I * F] + [I'* F] was presented to one eye, [I * F] + [I' * F] to the other, such that regions of the image that produced on-center cell responses in one eye produced off-center responses in the other eye, and vice versa.

Results: Participants continuously improved in a naturalistic object discrimination task over 20 one-hour sessions. Pre- and post-training tests suggest that performance improvements were due to two learning processes: learning to recognize objects with reduced visual information and learning to suppress contrast-reversed image information in a non-eye-selective manner.

Conclusions and Future Work: These results suggest that, with training, it is possible to adapt to the unnatural on- and off-cell population responses produced by electronic and optogenetic sight recovery technologies. To examine whether 'gamification' of training enhances perceptual learning, we are currently examining whether replacing the object discrimination task with a video game results in faster or larger perceptual learning of distorted input.

Biography: Rebecca Esquenazi is a Ph.D. candidate at the University of Washington under the supervision of Dr. Ione Fine. She received her bachelor's and master's degrees from California State University, Northridge in experimental psychology. In 2020 she was awarded a National Research Service Award (NRSA) to study the ways in which visual cortical plasticity influences perceptual experience of sight restoration technology users. Ultimately, she is interested in the potential for plasticity to aid prosthesis users in overcoming visual distortions caused by electronic and optogenetic sight restoration technologies, and the translational impact this research may have on the field.

Jacob Granley, M.Sc.
Bionic Vision Lab
University of California, Santa Barbara
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A Simple Computational Model of Phosphene Appearance for Epiretinal Prostheses

Jacob Granley and Michael Beyeler

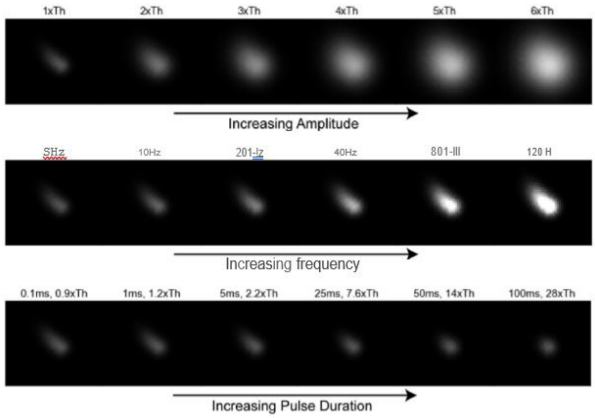
Purpose: A major outstanding challenge for retinal prostheses is to develop a computational model that can predict elicited phosphenes across a wide range of electrical stimuli. Here we present a phenomenological model that predicts phosphene appearance as a function of stimulus amplitude, frequency, and pulse duration. Whereas previous models focused on either spatial or temporal aspects of the elicited phosphenes in isolation, we describe a more comprehensive approach that is able to account for many reported visual effects.

Methods: It was previously shown that phosphene shape can be determined by the spatial activation pattern of retinal nerve fiber bundles (NFBs). Here, we expand on this technique to also produce phosphenes with accurate size, brightness, and streak length. Based on a variety of psychophysical and electrophysiological data, we include a number of simple equations that (i) adjust thresholds as a function of pulse duration, (ii) scale phosphene size as a function of amplitude, (iii) scale phosphene streak length as a function of pulse duration, and (iv) scale phosphene brightness with frequency and amplitude.

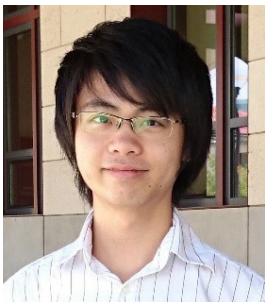
Results: Our model produces phosphenes that reflect a number of phenomena reported by epiretinal implant users (see Figure 1). Streaks are elongated along the underlying NFB, amplitude modulates both size and brightness, frequency modulates only brightness, and longer pulse durations lead to shorter streaks. We validate the model using psychophysical data from two independent studies, showing that it significantly outperforms previous models, and that it generalizes well to new data, even for novel stimuli on new electrodes.

Conclusion: We show that a model of axon NFBs along with a few simple equations representing reported visual effects can accurately predict elicited phosphenes for epiretinal prostheses. The model is available at https://tinyurl.com/axonmodel and is highly modular, allowing it to be easily extended to account for additional effects if data becomes available. The model can also be fit to a new retinal implant given a relatively small number of phosphene ratings and drawings. This is an important first step towards predicting visual outcomes in retinal prosthesis users across a wide range of stimuli.

Biography: Jacob Granley is a second year Ph.D. student studying in the Bionic Vision Lab under Dr. Michael Beyeler at University of California, Santa Barbara. His research focuses on using computer vision, machine learning, and computational modeling to help improve artificial vision technologies. His research interests include developing models for retinal and cortical artificial vision and using machine learning techniques to optimize electrical stimulation. Prior to UCSB, he earned his B.S. and, as part of a CACI machine learning research fellowship, his M.S. in Computer Science at Colorado School of Mines.



Figme J; Predicted phosphene appearance as a function of amplilude (fop), foequency (m iddle), and pulse duration (bouom) oom.trained. by data from Nanduri et al. (201 2 and eitz et al. {2 015



Elton Ho, Ph.D.
Stanford University
Stanford, California

A Real-time Image Optimization Algorithm for PRIMA Patients

Elton Ho1,2, and Daniel Palanker1,2

1Ophthalmology, 2Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA

Purpose: Priorities in restoration of central vision for patients with geographic atrophy include reading and face recognition. Current PRIMA implant with 100μm pixels provides black-and-white letter acuity closely matching the pixel size, but a greyscale rendering of the video stream from a camera appears to be insufficient for recognizing the facial features. Here we present a real-time image optimization algorithm to improve prosthetic vision in greyscale.

Methods: Prosthetic vision was simulated in three steps: (1) pixelating the image to 100 m-wide hexagons, (2) rounding pixel values to nine greyscale levels, and (3) Gaussian blurring. The radius for Gaussian blurring was determined in a psychophysics experiment with healthy participants to match the PRIMA patients' letter acuity. For real-time image optimization, each frame of the video stream was associated with a weight matrix matching the video frame dimensions. The element-wise product between the video frame and the weight matrix was then passed through the simulation of prosthetic vision. The loss function between the simulated prosthetic image and the original video frame was quantified with the multi-scale structural similarity index measure (MS- SSIM). To minimize the loss (i.e. to optimize the image quality), the weight matrix was then updated via gradient decent, and iterated until stabilized. The results of this algorithm were compared to (a) no processing, (b) a handcrafted image processing pipeline consisting of an opening filter, an erosion filter, and unsharp mask in sequence, and (c) a convolutional neural network.

Results: The perceptual blurring radius was found to be 110μm, which was more than double the electric field spread of a 100μm photodiode pixel with local returns. Compared to the other processing methods, the real-time image optimization demonstrated better image quality, robustness to micro saccades and image-implant alignment, invariance with feature scales, applicability to a wide range of image contexts, and required no training data. Images of 200x200 pix were typically optimized within 20 to 50 iterations.

Conclusions: Previous simulations of prosthetic vision typically underestimated the blurring radii, especially with pixels smaller than 100μm. The real-time image optimization significantly improves the recognition of simulated images. A dedicated application-specific integrated circuit (ASIC) can reduce the image processing time below 1ms per iteration.

Biography: Elton Ho received his Ph.D. from Stanford University. He is working with Dr. Daniel Palanker on developing a photovoltaic subretinal prosthesis. His involvements include implant circuit simulations, retinal network modeling with machine learning, ex vivo electrophysiology using a multielectrode array, visually evoked potential recordings in vivo, animal, and human behavioral assessments of prosthetic vision, and surgeries in rodents. He received his B.S. in Physics from University of Virginia.

Karst Hoogsteen, M.Sc.
Schepens Eye Research Institute
Boston, Massachusetts

Evaluation of Information Needs of Blind Pedestrians Performing Urban Mobility Tasks

Purpose: Neural prostheses may provide a promising means to convey useful information to blind travelers. Because the visual information provided by prosthetic devices is rudimentary, it is critical to determine what information to convey to blind travelers, when and how. We evaluated information needs in urban mobility tasks.

Methods: Thirteen cane-using participants, five of whom were early blind, took part in urban walking experiments. In the first experiment, participants were asked to voice their information needs in the form of questions to the experimenter. In the second experiment, participants were asked to score scene descriptions and navigation instructions, provided by the experimenter, in terms of their usefulness. The descriptions included a variety of objects with various annotations per object. Additionally, we asked participants to rank order the objects and the different descriptions per object in terms of priority and explain why the provided information is or is not useful to them.

Results: The results reveal differences between early and late blind participants. Late blind participants requested information more frequently and prioritized information about objects' locations. Factors of usefulness of scene descriptions, such as the level of detail, relative position, and what type of information is provided when describing an object (e.g., describing the location is more valued compared to the appearance) were identified. Participants explained how they (indirectly), used information, but frequently were unable to explain their ratings.

Conclusion: Our results distinguish between various types of travel information, underscore the importance of featuring these types at multiple levels of abstraction, and highlight gaps in current understanding of travel information needs. This information should pave the way towards developing image processing algorithms that prioritize useful travel information and foster the application of prosthetic devices as electronic travel aids for the blind.

Biography: Karst M.P. Hoogsteen is a low vision and blindness researcher with a focus on orientation and mobility at Schepens Eye Research Institute, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, United States of America and the Innovation Department Bartiméus, Netherlands.

Arathy Kartha, Ph.D.
Johns Hopkins University
Baltimore, Maryland

Object Rankings and Notification Preferences for an Object Finder System among People with Native and Artificial Ultra-Low Vision

Kartha, Arathy1 ; Sadeghi, Roksana1,2 ;Singh, Nikki5; Ju, Suyeon5; Chamberlain, Ryan3; Kramer, Kevin3; Gibson, Paul4; Lee, Soo Hyun1; Dagnelie, Gislin1

1. Wilmer Eye Institute, Baltimore, MD, United States. 2. Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States.3. Minnesota Health Solutions, MN, United States 4. Advanced Medical Electronics, MN, United States 5. Johns Hopkins University, Baltimore, MD, United States

Purpose: 1) To develop a list of everyday items based on the Common Objects in Context (COCO) dataset, that are highly useful among people with native and artificial ultra-low vision (ULV), so successful computer vision algorithms can be developed for object identification. 2) To investigate subjective and objective notification preferences among users with native and artificial ULV.

Methods: 10 participants with ULV (VA≤ 20/1600) and five Argus II users were given 150 items from the COCO dataset and asked to rate the objects as very useful, useful, neutral, not useful, definitely not useful and the scores were 2, 1, 0, -1, -2 respectively. They were also given an object (cellphone) finding task located at 10 random locations on a table, using speech and tone notification modalities. Accuracy and response times were recorded for each trial for a total of 30 trials/modality.

Results: Participants with native ULV and Argus II users rated more than 50% of the items on the dataset as useful and very useful. The objects that were reported to be most useful were similar in both groups, and the top five useful objects reported that would benefit from using an object finder device were phone, empty seat, remote control, person and toilet. The category that was rated highest was person and the category with the lowest rating was animal (Fig 1). All participants performed at higher than chance level for both speech and tone notifications irrespective of their level of residual vision (between 1.4 and 3.5 log MAR). Overall, there were no significant differences in accuracy and speed between speech and tone notifications.

Conclusions: We developed a priority list of useful objects from everyday life based on the COCO dataset among people with native ULV and Argus II users that could be identified using an object finder. Using the subjective ratings from this study, performance measures will be developed to determine the effect of an object finder system on functional performance and accessibility in people with ULV and visual prostheses. Future studies will compare the effect of different multisensory functional performance in people with ULV and visual prostheses.

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Commercial Relationships: Arathy Kartha: Code N, Roksana Sadeghi: Code N, Nikki Singh: Code N, Suyeon Ju: Code N, Soo Hyun Lee: Code N, Gislin Dagnelie: Code N Kevin Kramer: Code E , Ryan Chamberlain: Code E Paul Gibson: Code E, Minnesota Health Solutions, MN, USA
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Biography: Arathy Kartha received her Ph.D. in pediatric vision rehabilitation from Queensland University of Technology, Australia. She is currently a postdoctoral research fellow in Dr. Gislin Dagnelie's lab at Johns Hopkins Wilmer Eye Institute. Her area of interest is low vision rehabilitation. She is interested in studying about methods to improve visual performance and functional vision in people with visual prosthesis and ultra-low vision.

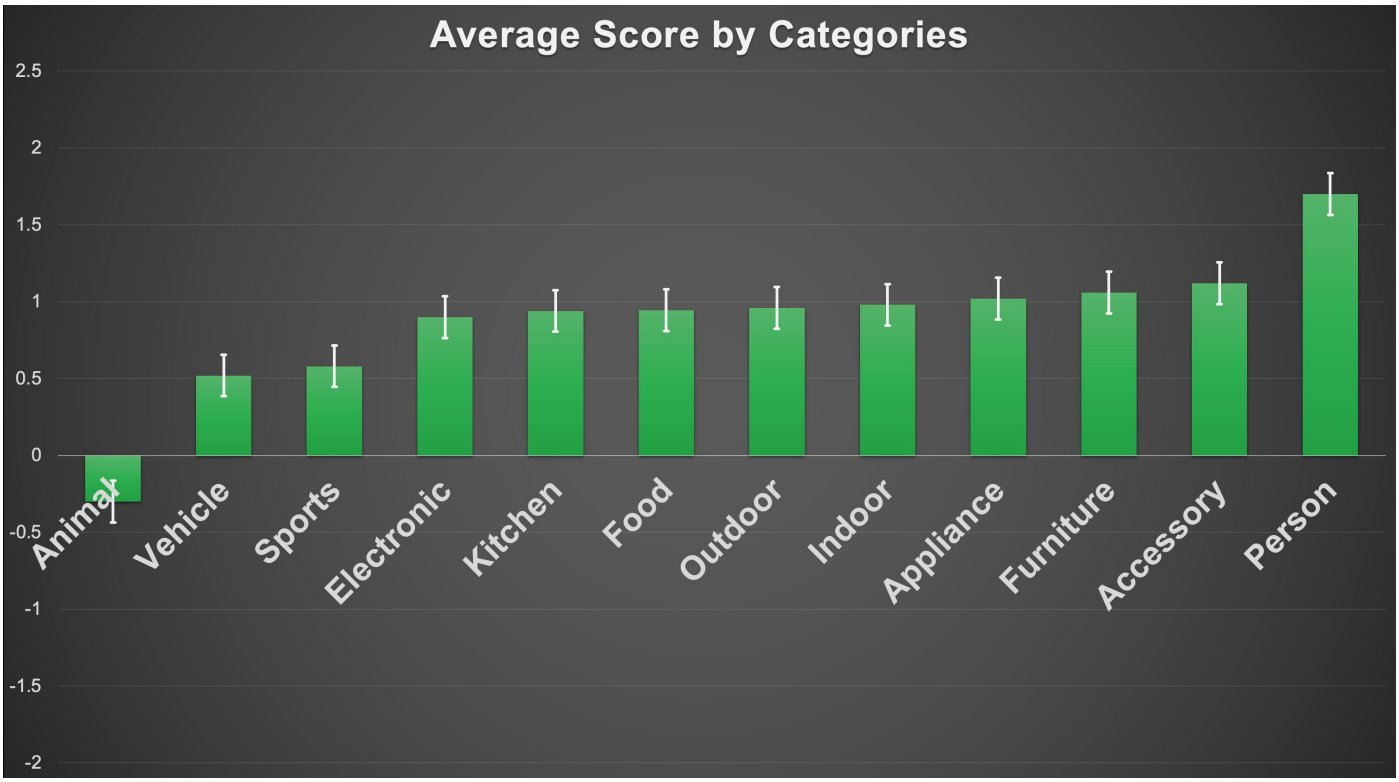

Figure 1. Average usefulness scores by category. Error bars represent standard error of the mean.

Cem Kesim, M.D.
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Biocompatibility and Neural Stimulation Capacity of Aluminum Antimonide Nanocrystal Integrated Biointerfaces for Use in Artificial Vision

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Purpose: Colloidal inorganic nanocrystals have great potential as photosensitive bio interfaces that might be used as retinal stimulation devices. We introduced the aluminum antimonide nanocrystals (AlSb NCs) as a cell interfacing layer for light-induced capacitive neural stimulation in the blue spectrum.

Method: A four-layer photovoltaic bio interface was fabricated by sequential planar deposition of indium tin oxide (ITO), zinc oxide (ZnO), organic poly(3-hexylthiophene) (P3HT) and AlSb NCs that is excitable under 445 nm blue LED illumination. Biocompatibility tests were performed in vitro on rat primary hippocampal neurons (PHN) and in vivo by subretinal implantation of the bio interface into adult rat eyes. In vitro electrophysiology for AlSb NCs based photo stimulation of PHN were measured by whole cell patch clamp method.

Results: The AlSb NCs based bio interface generated a photovoltage increase from 52 to 98 mV.cm-2 with a rise time of ~55 s upon stimulation. MTT viability assay showed no significant decrease in PHN metabolic activity (P>.05). No increase of TUNEL-positive cells was observed in bio interface implanted retinas when compared with sham group (P>.05). The bio interface effectively induced action potential in PHN with >90% success rate when stimulated by LED illumination frequencies up to 10 Hz.

Conclusion: AlSb NCs based bio interfaces hold high promise for future bioelectronics. With their high performance and biocompatibility, AlSb nanocrystals prove to be strong candidates for nanoengineered protheses to rescue vision.

Biography: Cem Kesim, M.D. is an ophthalmologist at Koç University School of Medicine, Department of Ophthalmology in Istanbul, Turkey. He works as a researcher in Koç University Research Center for Translational Medicine in a research team which focuses on the field of photo stimulation-based bio interfaces.

Kathleen Kish, M.Sc.
University of Michigan
Ann Arbor, Michigan

Developing Realistic Models of Retinal Stimulation

Kathleen E. Kish, James D. Weiland
Biomedical Engineering, University of Michigan, Ann Arbor, MI

Purpose: Computational models are an important tool for investigating the mechanisms of retinal stimulation. However, most models simplify the retina's bulk tissue and cellular structure and omit details of the retinal implant. In this study, we investigate how increasing anatomical realism affects model predictions by evaluating three common assumptions.

Methods: To model the retina's response to stimulation, we coupled a three-dimensional finite element model (FEM) to multi-compartment cable models of retinal ganglion cells (RGCs). We used finite element analysis to calculate the electric potential generated by the stimulating electrode throughout the retinal tissue, and we used cable models to estimate the neural response. We conducted sensitivity analyses to assess the impact of improving model realism in three areas. First, we evaluated the influence of axon morphometry on RGC activation thresholds. Rather than using an idealized straight axon, we extracted trajectories directly from fluorescence images of mouse retina. Secondly, we compared an FEM of the whole eye and extraocular ground to an FEM localized around the implanted region. Finally, we compared a canonical FEM with constant retinal thickness and uniform electrode retina distance to patient-specific FEMs reconstructed from optical coherence tomography (OCT) images.

Results: In our first experiment, we determined that RGC cable models are sensitive to changes in the ascending axon trajectory between the soma and nerve fiber layer. On the other hand, RGC cable models are robust to trajectory deviations in the plane parallel to the disc electrode's surface. In our second experiment, we found that including an explicit model of the extraocular ground is not critical for predicting retinal activation, changing thresholds by less than 2%. Finally, we found that patient-specific FEMs reconstructed from imaging data capture relevant geometric and physiological factors (e.g. retinal thickness, fibrotic tissue, electrode position) that alter the electric fields and resulting neural activation.

Conclusion: Developing realistic neurophysiological models of retinal stimulation can improve predictions of retinal activity in response to various electric stimuli for individual patients. In the future, we will use these realistic models to optimize retinal stimulation parameters. Personalized device programming efforts are critical for improving prosthesis performance.

Biography: Kathleen Kish is a Ph.D. student in Biomedical Engineering at the University of Michigan. She received her B.S. in Engineering (biomechanical concentration) from Hope College in 2018 and her M.S. in Biomedical Engineering (neural engineering and bioelectric concentration) from the University of Michigan in 2020. Her research focuses on creating biological computational models of retinal stimulation. The primary goal is to optimize retinal stimulation strategies, using a patient-specific tissue activation modeling approach, where model predictions are correlated with clinical effects. This work will provide a framework to develop, evaluate, validate, and translate novel approaches for improving patient outcomes (e.g., visual acuity, implant efficiency) during retinal stimulation.

Beomseo Koo, M.S.
University of Michigan
Ann Arbor, Michigan

Surgical Procedure for Chronic Rodent Epiretinal Implant Model

Purpose: Clinical visual prosthesis devices have found success in extracting user-reported feedback data to improve device design, stimulation strategies, and training regimens. Animal models, with its ability support large sample sizes, can provide supporting information with neural signals and behavioral assays evoked from electrical stimulation of the retina. However, there has been little work to study chronic epiretinal prosthesis implants in the in vivo rat animal model. Here we detail an epiretinal implant designed for rat studies and the surgical procedure associated used to achieve a study duration of 4-weeks with weekly electric stimulation response measurements.

Methods: We designed a replicable monopolar stimulation electrode for retinal implant protocol development. We also tested a collaborating lab's passive parylene epiretinal implant. For the monopolar electrode, we bred a retinal degeneration model (P23H-LE) by crossing an autosomal-dominant SD-Tg(P23H)1Lav homozygote with a Long-Evans rat. At post-natal day 150, a monopolar electrode was implanted and weekly electric stimulation response recording was conducted for four weeks. Neural response was recorded with stainless steel recording screws implanted above the primary visual cortex. Electrically evoked responses were evoked with an external stimulator. Passive parylene implant testing was done in Long-Evans rats. Retinal implant position was verified with optical coherence tomography (OCT) centered at the optic nerve.

Results: Implanted Long-Evans (passive parylene, N=1) and P23H-LE rats (monopolar electrode, N=4) showed no behavioral change and nominal eye condition throughout the four week implant duration. For monopolar electrode implants, interconnecting wire breakage noted in earlier pilot experiments was solved with improved surgical technique. Impedance of the monopolar electrode was stable throughout the 4 week experiments. OCT images showed the monoopolar implants remained intraocular for four weeks, but some damage to the retina was noted. Weekly electrically evoked response was successfully measured for one of the monopolar electrode implants and this signal was consistent for all four weeks. The passive parylene array showed a stable epiretinal position at week one and week four of implant assessed with OCT.

Conclusion: Epiretinal implant in a rat animal model is feasible and can be adapted to a chronic electrophysiology protocol. Implants designed for such purposes need only require consideration of the rat's small ocular globe. A parylene implant may be better tolerated by the eye due to its relative flexibility (vs. the monopolar wire). When combined with an appropriately sized microstimulator, animals implanted with these epiretinal implants may be used for awake, electric stimulation response measurements and for behavioral experiments.

Biography: Beomseo Koo is currently a Ph.D. student in James Weiland's Bio Electronic Vision Lab and a Ph.D. student in Biomedical Engineering at the University of Michigan. He received his B.S. in Bioengineering at George Mason University and his M.S. in Biomedical Engineering at the University of Michigan. Beomseo is an animal surgeon, histology, neuro-electrophysiology specialist in research for retinal and cortical vision prosthesis. He has previous experience in research in neuro inflammation response from neural implants.

Soo Hyun Lee, B.S.
Johns Hopkins University
Baltimore, Maryland

Variability in Absolute Phosphene Mapping Techniques: Finger vs. Gaze Coordinates

Purpose: Visual perception can be created by sending electrical stimulation pulses to intracortically implanted electrodes, with the goal to generate small points of light called phosphenes. The hope is that these phosphenes can be combined to generate coherent images for blind subjects. We seek to develop reliable methods to create phosphene maps for blind subjects by simulating phosphenes in normally sighted subjects.

Method: Participants were seated at a table facing the center of a 36" diameter concave cap of a sphere with 24" radius, so their left index finger could comfortably reach the entire left half of the curved cap surface. A VIVE Pro Eye headset was used to record head and eye movements, and a G4 Polhemus tracker recorded the finger position. The center of the cap was marked by a bump dot to facilitate centering the finger while wearing the headset. At the start of each trial, the participant touched the center position while looking at a green dot shown in the headset, aligned with the tactile center dot. When a white dot, representing a phosphene, appeared in the left half of the screen, the participant was verbally prompted to point to the perceived dot location by moving their left index finger while maintaining central fixation. The white dot then disappeared, along with a verbal prompt to orient either the eye gaze or the head to the remembered dot location while still pointing. Trials were carried out for 32 dots randomly distributed at up to 35° in the lower 120°of the left hemifield and repeated three times in a session.

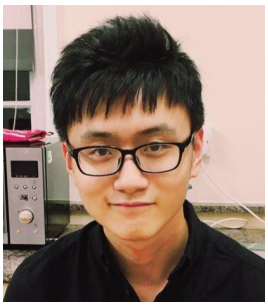
Results: Until now, six participants with normal vision have been tested. The collected finger data were affected by magnetic field distortion, so a spline fit was used to correct the distortion. Finger position pitch and yaw angles in degrees were calculated and showed a coefficients of variation of 21.9±2.2% and 21.5±1.5% (mean±SD, across subjects) respectively. Finger tracking data were found to be much more stable than gaze data; head tracking data are currently being collected and appear to be more stable than gaze data. We continue to examine the gaze data for possible sources of variability.

Conclusion: The development of intracortical implants is in its early stages. Finger pointing data have until now been the only method reported for phosphene mapping; adding either gaze or head data may provide an independent estimate of phosphene locations. Even though our initial attempts at using gaze data have proven unsatisfactory, we continue to explore methods to reduce the variability.

Biography: Soo Hyun Lee received her B.S. in Neuroscience with a minor in Computer Science from Johns Hopkins University in May 2020. She joined the Dagnelie lab in October 2020 and is highly interested in working with medical devices.

Authors: Soo Hyun Lee, Liancheng Yang, Haichun Sun, Krishna Sargur, William Diaz, Suyeon Ju, Roksana Sadeghi, Arathy Kartha, Gislin Dagnelie

Commercial Relationships Disclosure: Soo Hyun Lee: Commercial Relationship: Code N (No Commercial Relationship) | Liancheng Yang: Commercial Relationship: Code N (No Commercial Relationship) | Haichun Sun: Commercial Relationship: Code N (No Commercial Relationship) | Krishna Sargur: Commercial Relationship: Code N (No Commercial Relationship) | William Diaz: Commercial Relationship: Code N (No Commercial Relationship) Suyeon Ju: Commercial Relationship: Code N (No Commercial Relationship) | Roksana Sadeghi: Commercial Relationship: Code N (No Commercial Relationship) | Arathy Kartha: Commercial Relationship: Code N (No Commercial Relationship) | Gislin Dagnelie: Commercial Relationship: Code N (No Commercial Relationship)



Yu Liu, M.Sc.
Neuroprosthetics Lab, Newcastle University
Newcastle, United Kingdom

Newcastle Visual Cortical Prosthesis – Control System

Additional contributions from the Institute of Neuroscience, Newcastle University, and the wider CANDO project team at Newcastle, UCL, Imperial College.

The Newcastle Visual Cortical Prosthesis project aims to create an optogenetic form of visual cortical prosthesis. We have been developing two forms of probes – low resolution planar probes and higher resolution optical probes for optical stimulation of the cortex. We also have an operational ASIC (We are developing in our sister project CANDO) for driving these probes. In this work, we want to give an update on our subcutaneous control unit and information transmission software. Our subcutaneous control unit has the functions of wireless power transmission and wireless data transmission.

Our control unit obtains power from external hardware through inductive coupling coils to provide power to various modules on the PCB, and its built-in energy management module also provides driving power for our probes. It receives the real-time image stream transmitted by external hardware through Bluetooth connection, and after further processing, it controls the optrode array to flash according to the content of each frame of image by synchronizing the SPI signal with the driving ASIC. The original image has been processed by methods such as anisotropic diffusion algorithm, edge detection, pyramid resizing, and stimulator mapping to optimize the recognizability of the image while reducing the resolution. And we used run length coding to encode in the Bluetooth transmission process to further compress the size of the image stream. For each frame of image to be displayed, the control unit dynamically allocates the power-on time of each LED on the optrode to ensure that the total drive current flowing through the optrode array does not exceed the maximum threshold that the brain tissue can tolerate.

Biography: Yu received his B.Eng. degree (Automation & Control) from Jilin University, China, and M.Sc. degree (Wireless Embedded System) with distinction from Newcastle University, UK. He is currently Ph.D. student under supervision of Dr. Patrick Degenaar in neuro-prosthesis lab, Newcastle, with a main focus on the optogenetic visual prosthetics.

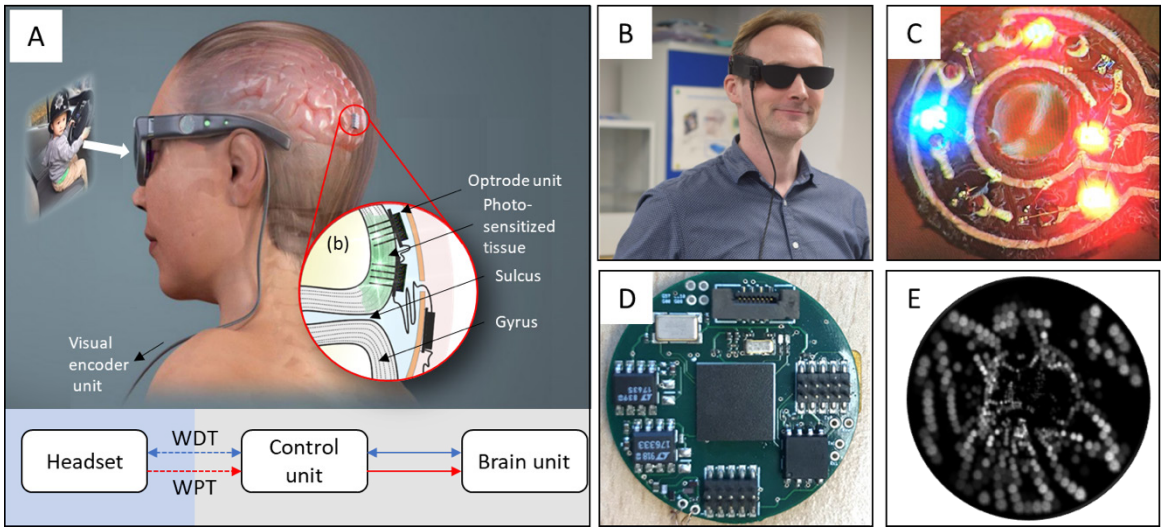


Fig. A. The concept of the visual cortical prosthesis. B. The headset unit. C. The brain unit. D. The control unit. E. The processed image.

Keith Ly, M.Eng.
University of New South Wales
Sydney, Australia

A Generic Network Model of Neural Retina for Investigating Retinal Responses to Electric Stimulation.

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Rationale: A key reason for the poor performance provided by current state-of-the-art retinal stimulators is limited knowledge of the neural code of vision. In this study, we developed a generic computational network model of neural retina consisting of three retinal pathways: ON cone, OFF cone, and rod pathways. Given that these pathways serve unique roles in visual signal processing, this study represents an important step in simulating and understanding the retinal neural code, providing a platform for investigating retinal network responses to electric stimulation.

Method: A neural retina network computational model was implemented in NEURON 7.2. Three retinal pathways were reconstructed based on unique synaptic connections and gap junctions between different retinal neurons reported in in-vitro retinal studies [1]. Individual rods, cones, horizontal cells, ON and OFF cone bipolar cells, rod bipolar cells, AII amacrine cells, ON and OFF ganglion cells were simulated using single-compartment models. A retinal tissue of 0.143 mm2 was reconstructed based on reported immunochemistry data [2]. The outer retina was simulated by a cone array of 57 cells, a rod array of 1742 cells and seven horizontal cells. The inner retina was simulated by 199 bipolar cells, Five AII amacrine cells and 31 ganglion cells.

Results: Simulated retinal cell responses closely resembled in-vitro electrophysiological data [3]. Given a photocurrent stimulus with an amplitude of 40 pA with a duration of 400 ms, the model produced a 12 mV hyperpolarisation in the cones whilst the rods exhibited a 16 mV hyperpolarisation, where the difference was due to the inhibitory feedback synapses between cones and horizontal cells. Horizontal cells produced a rapid 27 mV hyperpolarisation with a slow recovery to baseline potential at -52 mV. ON cone bipolar cells exhibited a 36 mV depolarisation, whilst the OFF cones exhibited a 30 mV hyperpolarisation. Both ON and OFF ganglion cells demonstrated characteristic physiological responses to light stimuli.

Conclusion: Our neural retinal network model was able to reproduce retinal cell responses to both electric and light stimuli, providing a platform for improved understanding of normal and diseased retinal function, as well as further optimization of retinal prosthetic devices. Planned extensions of the model includes simulation of functional remodelling at various stages of retinal degeneration, allowing translation to clinical applications.

References:

[1] Demb et al. (2015), "Functional Circuitry of the Retina", Annu. Rev. Vis. Sci., 1:263–89.
[2] Jeon et al. (1998), "The Major Cell Populations of the Mouse Retina", The Journal of Neuroscience, 18(21), pp. 8936-8946
[3] Tsai et al. (2017), "Survey of Electrically Evoked Responses in the Retina – Stimulus Preferences and Oscillation Among Neurons", Scientific Reports, 7, 10.1038/s41598-017- 14357-1

Biography: Mr Keith Ly is currently a Ph.D. Candidate with the Graduate School of Biomedical Engineering at UNSW Sydney. He received his B.E. in Mechatronics Engineering and M.E. in Biomedical Engineering at UNSW in 2019. Ly's research focuses on understanding (1) how retinal electrophysiology could be influenced under degeneration conditions, (2) how individual retinal cell and retinal neuronal network respond to electrical stimulation, and (3) how electrical stimulation parameters could be optimised to maximize the perceptual efficacy of retinal implants. Ly is currently developing a computational model of the retinal neuronal network to study the signal processing in both healthy and diseased retina. He will use this model to expand our understanding of how artificial stimulation interacts with retinal tissue with the hope of improving the quality of the elicited neural activity, therefore improving the overall performance of retinal neuroprostheses.

Negin Nadvar, M.S.
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Effect of Tunnel Vision Blindness on Brain Connectivity

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1 Biomedical Engineering Department, University of Michigan
2 Department of Psychology, University of Michigan
3 Department of Ophthalmology and Visual Sciences, University of Michigan
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Purpose: Understanding how partial and full blindness affect the brain functional networks is informative and crucial for sight restoration. Prior studies have revealed that loss of visual input in the blind leads to reduction of resting state functional connectivity (FC), not only within the visual cortex, but also cross-modally between the visual and other sensory cortices. It is not clear when such alterations occur during the process of blindness. In this work, we aim to uncover whether partial sight deprivation (and not necessarily full blindness) is sufficient to induce such functional changes.

Method: Four healthy controls (HC) and seven subjects suffering from tunnel vision due to Retinitis Pigmentosa (TVRP) were recruited at University of Southern California for resting state functional MRI acquisition; no age difference between the groups ($P > 0.2$). FC maps were created with seeds in the left and right V1 and V5 areas in the visual cortex, p-FDR (False Discovery Rate)<0.05. Group differences in FC between HC and TVRP were calculated, and corrected using Gaussian Random Field, p-FDR<0.05. Extent of FC was also calculated as the percentage of voxels in a selected target region of interest with significant connection to the seed.

Results: TVRP-vs-HC group contrast identified: 1) 1 cluster, overlapping with Fusiform gyrus (FusG), that had significantly less FC with V1 (mean effect size: 0.22 vs 0.52 for V1R seed and 0.20 vs 0.54 for V1L seed), 2) 1 cluster, overlapping V2 and cuneus that had significantly less FC with V5 (mean effect size: 0.13 vs 0.43 for V5R seed and 0.16 vs 0.47 for V5L seed). Although no significant group-level change in V1 FC to visual areas and somatosensory Post Central gyrus (PostCG) was observed, V5-PostCG FC was smaller in TVRP vs HC: 38% vs 68% for V5R and 41% vs 70% for V5L seeds.

Conclusion: Multiple studies have shown reduced FC of V1 to visual and sensory areas upon full blindness. Our results showed that in TVRP, these connections are not altered, despite the observed decreasing FC trends. Instead, connection with FusG, a face recognition region, is affected earlier, indicating that vision loss may affect the visual involvement of the 'what' (ventral) visual stream long before the 'where' (dorsal) visual pathway. Additionally, V5 (and not V1) FC to PostCG tended to be smaller in TVRP. As a result, visual-somatosensory cross-modal changes in blindness may be inclined to initially start at higher levels of visual cortex before their realization in the primary visual area.

Biography: Negin Nadvar is a Ph.D. candidate in BioElectronic Vision Lab at the Department of Biomedical Engineering at the University of Michigan. Her research area is on the effect of sight restoration with retinal prosthesis implants on brains of late-blind individuals. She utilizes functional MRI techniques to evaluate cross-modal plasticity and functional connectivity in the sight-restored. Her undergraduate degree is in (bioelectrical) biomedical engineering where she worked on patients' data mining and manipulation. Her master's education is in electrical engineering with a focus on signal processing and communication. She worked at Stryker Instruments for 3.5 years as an electrical engineer working in R&D on new product development studies for heavy duty drills/saws and smart high-temperature batteries. She also has two years of experience in instructing freshman and sophomore courses in electrical engineering. Negin is currently pursuing her Ph.D. education in neural engineering to learn more about the fascinating complex inner work of the brain and how it functions as a network.

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Japanese Artificial Vision Institute
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Effect of Spike-shaped Array on Electrode Position Fluctuation of Suprachoroidal Retinal Prosthesis

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Purpose: Visual reconstruction using retinal prostheses requires evoking pseudolight sensations (phosphene) by electrical stimulation. However, electrode position changes over time [P. J. Allen, et al. IOVS 2019, Y. Terasawa, et al. IOVS 2017], and it is difficult to evoke phosphene when the electrode is moved away from the macula. In this study, we evaluated whether an electrode array, equipped with dorsal protrusions (spike-shaped array; Fig. 1), can reduce movements of the electrode.

Methods: A control array without dorsal protrusions or spike-shaped array was implanted in the scleral pocket of rabbits (n = 6). Both arrays had platinum electrodes. The distance and rotation angle between the original electrode and shifted positions was estimated using superimposing scanning laser ophthalmoscopy (SLO) images immediately after the surgery and at first week, first month, second month, and third month postoperatively. To superimpose the images, the coagulation plaques or black dots around the optic nerve papilla were used as reference points.

Results: SLO imaging showed movement of the electrodes. Directions of electrode movements were not uniform. The control and spike-shaped arrays shifted a mean of 0.37 ± 0.06 mm (n = 4) and 0.23 ± 0.10 mm (n = 6), respectively, between the first postoperative week and first postoperative month ($p < 0.05$, independent t-test; Fig. 2). However, no significant difference was found between the control and spike-shaped arrays after the second postoperative month. In total, within three months after implantation, the control and spike-shaped arrays shifted a mean of 0.83 ± 0.02 mm (n = 4) and 0.68 ± 0.11 mm (n = 6), respectively. The total rotation angle within three months after implantation was a mean of 26 ± 6° (n = 2) for the control array and a mean of 23 ± 17° (n = 2) for the spike-shaped array, with no significant difference.

Conclusion: The movement distance of electrodes in the spike-shaped array was smaller than that of the control array. However, the spike-shaped array had little effect in suppressing the electrode movements for over a long period of time. This suggests that the tension applied to the cable is believed to be one of the reasons for the movement of the electrodes. Therefore, it is necessary to determine how much tension from the cable is involved in the movement of the electrodes.

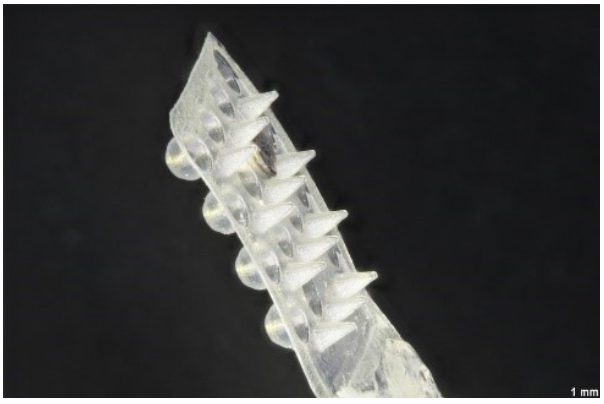

Fig. 1. Spike-shaped array

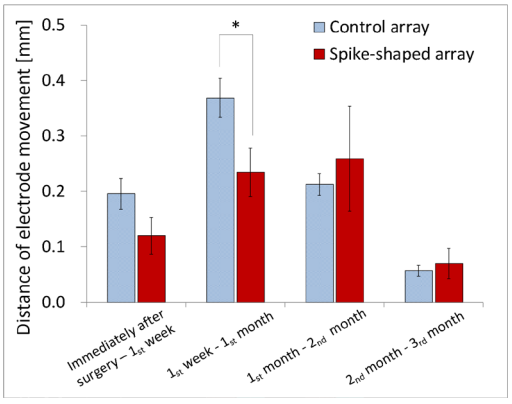

Fig. 2. Distance of electrode movement in each period

Andrea Neviani, Ph.D.
University of Padova
Padova, Italy

High-efficiency CMOS-based Wireless Power and Data Transceiver and Stimulator for Artificial Retina

Purpose: The conventional circuits for artificial retina system has diode-based power transmission and recovery circuit, showing low power transmission efficiency and high stimulation power consumption. In this work, CMOS-based wireless power and data transceiver and switching reference-based stimulation circuit was investigated to maximize output power delivery.

Methods: A transformer using near field wireless power transmission was designed to deliver maximum power with a limited size receiver coil. In consideration of low coupling by body tissue between transceiver, a robust power recovery circuit is designed for k factor that can deliver target power and voltage. For data transmission, pulse delay modulation (PDM) was used to get higher data rate. By detecting delay between original power carrier interference and received signal from data receiver part, data recovery procedure can be followed. A channel-sharing stimulator is designed so that one current generator can stimulate four electrodes continuously. This allows each electrode to be stimulated in chronological order to reduce instantaneous maximum power consumption. Also, switching reference circuit was suggested to get large output compliance voltage under low supply voltage.

Results: By tuning the transformer, we designed a power recovery circuit delivering 5V output voltage and nominal 40mW was delivered to the output with 3V of input voltage without additional matching network at coupling condition of k = 0.037. By using PDM scheme for data recovery, data rate of 13.56Mbps which is same as working industry-science-medical frequency 13.56MHz can be achieved. With channel sharing technique, one current generator designed to sequentially stimulate four electrodes, resulting in reduction of instantaneous maximum power consumption of the stimulator stage by a quarter. Moreover, suggested switching reference circuit allows us to get large output compliance voltage up to ± 4V with low supply voltage as 5V.

Conclusions: A near field wireless power transceiver focused on delivering power efficiently in harsh coupling condition was designed, and target output power could be achieved regardless of weak coupling condition ($k \approx 0.03$) compared to existing artificial retina stimulation circuit. Pulse delay modulation (PDM) scheme was adopted for wireless data delivery to achieve high data rate. Also switching reference method was suggested for large output voltage compliance under low supply voltage condition.

Biography: Andrea Neviani received a "Laurea" degree (cum laude) in Physics from the University of Modena, Italy in 1989, and the Ph.D. degree in Electronics and Telecommunication Engineering from the University of Padova, Italy, in 1994. In the academic year 1993/94 he was a "graduate student" at the University of California at Santa Barbara, as part of his Ph.D. program. Since March 2016 he was Full Professor of Electronics at the University of Padova, where he earlier held the position of Associate Professor (1998 - 2016) and Research Associate (1994 - 1998). From November 1998 to November 1999, he was visiting engineer at Rutherford Appleton Laboratory, Oxfordshire, UK. Andrea Neviani served as an Associate Editor of the IEEE Transactions on Circuits and Systems I from 2010 to 2012 and has been a member of the IEEE Technical Committee on Circuits and Systems for Communication from 2008 to 2016. In 2014 he was invited to serve in the Technical Program Committee of the European Solid-State Circuits Conference (ESSCIRC). Since March 2017 he is Head of the Ph.D. School in Information Engineering of the University of Padova.

Denise Oswalt, Ph.D.
University of Pennsylvania
Philadelphia, Pennsylvania

Multi-electrode Stimulation Evokes Consistent Spatial Pattern of Phosphenes and Improves Phosphene Mapping in Blind Subjects Implanted with the Second Sight Orion Cortical Visual Prosthesis

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a Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA
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d Second Sight Medical Products, Sylmar, California
e Department of Neurological Surgery, University of Texas Southwestern, Dallas, TX

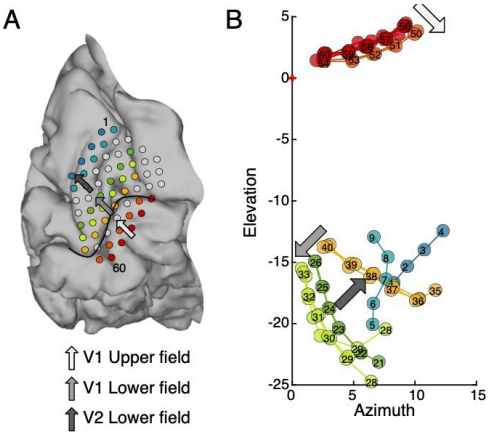
Purpose: Visual prostheses are envisioned to operate by combining phosphenes produced by stimulation of individual electrodes to produce a percept of an image. This strategy requires efficient and reliable methods for mapping individual phosphenes. We examined different mapping techniques in two blind subjects (BS1 and BS2) who are participants in the clinical trial of the Orion visual cortical prosthesis.

Methods: Two fixation strategies were tested. For unimanual fixation, subjects placed a single index finger on a tactile fixation point. For bimanual fixation, subjects overlaid their right index finger atop their left on the fixation point. Two mapping strategies were tested. For absolute mapping, a single electrode was stimulated on each trial while for relative mapping, dynamic sequences of stimulation were delivered to three to five electrodes on each trial.

Results: Bimanual fixation resulted in lower variability in phosphene localization than unimanual fixation (BS1: 4.0±2.6° vs. 19±4.7°, $t(79) = 7$, $p \ll 0.001$; BS2 4.1±2.0° vs. 12±2.7°, $t(65) = 7$, $p \ll 0.001$). Multi-point relative mapping had similar baseline precision to absolute mapping (BS1: 4.7±2.6° vs. 3.9±2.0°; BS2: 4.1±2.0° vs. 3.2±1.1°) but improved significantly when trial-to-trial errors were removed. Translational, rotational, and scaling errors were observed, with translational errors accounting for a majority of the incongruity. Multipoint sequences can capture basic retinotopic organization of visual cortex but tends to regularize distance between perceived phosphenes (see Figure). Fitting a logarithmic map to these data can address this issue and generate a final map estimate.

Conclusion: Relative mapping methods, combined with bimanual fixation resulted in the most precise and consistent estimates of phosphene location.

Biography: Denise Oswalt is a postdoctoral researcher in the Department of Neurosurgery at the University of Pennsylvania in the lab of Daniel Yoshor. Her degree is in Biomedical Engineering and her research background is primarily in electrical stimulation of early visual cortex in human and nonhuman primates. Her research interests are focused on developing stimulation strategies to convey salient visual imagery through direct electrical stimulation of cortex as well as better understanding of how low-level stimulation features translate into patterns of cortical activation. Additional interests revolve around implementing biomimetic stimulation strategies to attempts to induce more naturalistic cortical activation patterns.



A. Discs show electrode locations on the medial wall of the occipital lobe. B. Location of individual phosphenes, colored and numbered to correspond to each electrode in panel A. Electrodes were stimulated in sequences selected from individual rows in the array, corresponding to different colors. The arrows on the visual field map indicate the progression in the visual field for phosphenes evoked by the corresponding electrode sequences in the V1 upper field representation (light gray), V1 lower field (median gray), V2 lower field (dark gray).

Financial Disclosure: JD and UP are employees of and have financial interests in Second Sight Medical Products, Inc.

Uday Patel, Ph.D.
Second Sight Medical Products
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Long-term Reliability of the Orion Visual Cortical Prosthesis

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2University of Texas Southwestern
3University of Pennsylvania
4Alfred E. Mann Foundation
5University of California, Los Angeles

Purpose: To evaluate the reliability of the Orion Visual Cortical Prosthesis over time.

Methods: Six subjects who are bilaterally blind with bare light or no light perception due to non-cortical etiology were implanted with the Orion Visual Cortical Prosthesis between February 2018 and February 2019. The Orion implant electrode array consists of 60 non-penetrating electrodes with diameters of 2 mm and center-to-center distances of 3 mm. At the time of implantation, all devices had between 58 and 60 enabled electrodes. Patients are allowed to use the device at home for a limited time each day, typically for up to two hours.

Electrode impedance measurements are performed each time the device is powered on and additionally each time the patient participates in psychophysical testing. Electrodes are automatically disabled if impedance values fall out of specification by exceeding 16 kΩ.

Results: For five of the six implants, impedances for all electrodes enabled at implantation remained in the specified range thus far. One implant has experienced automatic disabling of some electrodes. These electrodes are all confined to a single layer of the array which contains 30 electrodes. However, the implant is still functional and the subject does experience some perception on the remaining 30 electrodes. A second implant has experienced impedance fluctuations over time that are more dramatic than most, and seem to be correlated with changes in perception. However, the device itself is functioning and does not appear to be the cause of these changes.

Conclusions: The first-in-human clinical trial of the Orion Visual Cortical Prosthesis has demonstrated long-term reliability of over three years for the majority of our implants. While impedance values for electrodes have exhibited some variability over time, no trends that may indicate progressive failure have been observed.

Biography: Uday Patel, Ph.D., joined Second Sight in 2008. His support of their clinical research efforts led to the Humanitarian Device Exemption for the Argus® II Retinal Prosthesis System, a first-of-its-kind device that uses electrical stimulation to provide useful vision to blind individuals severely impacted by retinitis pigmentosa. He supported the early commercialization efforts for the Argus® II before transitioning to the role of Principal Scientist for the Orion Visual Cortical Prosthesis System. He received his doctorate from UCLA in the NeuroEngineering Training Program studying computational modeling of the networks responsible for vertebrate locomotion. Financial Relationships: JD and UP are employees of and have financial interests in Second Sight Medical Products, Inc. This work is funded by NIH grant 5UH3NS103442.

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Optimized Stimulation Paradigms for Electrical Retinal Implants: The Combination of Voltage Pulse Polarity and Reference Electrode Distance Yield Distinctive Ganglion Cell Response Patterns.

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Purpose: Electrical (e-) subretinal implants can generate visual sensations in blind patients but with limited temporal and spatial resolution, e.g., due to cell response fading. For improvement of artificial vision, a better understanding of the limiting neurobiological factors is crucial. Hence, within this study we investigated combinations of different voltage strengths, polarities of biphasic pulses, and distance to the reference-electrode in a search for a novel e-stimulation (e-stim) paradigm that reduces cell response fading.

Methods: The outer retina of the blind rd1 mouse (retinitis pigmentosa model) was e-stimulated in subretinal configuration with a multi-electrode array (59 electrodes, 10 m diameter and 40 m spacing); the evoked ganglion cell (GC) responses were recorded by methods of calcium-imaging. A large range of e-stim parameters was investigated including pulse polarity of the biphasic stimulus (cathodic vs. anodic first), incrementing e-stim voltage (basic voltage (anodic phase) 500 - 2500 mV, 500 mV steps), varying voltage balance between the anodic and cathodic pulse phase (200 mV steps) and changing the position of the return electrodes (a single large remote (2 mm distance) reference electrode vs. multiple neighbouring (40 m distance) reference electrodes.

Results: (1) A stronger GC activation and a lower e-stim voltage threshold was observed for e-stim with cathodic-first pulse polarity. Additionally, multiple nearby references electrodes to the stimulation electrodes evoked (2) stronger GC responses (3) with significantly shorter response decay times. (4) A stronger cell response fading was promoted by cathodic-first stimulation and high voltage disbalance between the cathodic and anodic pulse phase. (5) The GC activation between both return configurations was equal across a distance of 60 m. However, less cells were activated when using nearby reference electrodes.

Conclusion: The study covers systematically and extensively specific combinations of different e-stim parameters, which allowed the investigation of distinctive response patterns of GCs in calcium-imaging responses evolving into an enhanced subretinal e-stim paradigm to reduce cell fading. These findings indicate great, not yet fully used, potentials for improvement of artificial vision mediated by subretinal e-implants.

Biography: Lucia Peiroten completed her M.Sc. in Neurobiology at the University of Tuebingen, Germany. She is currently a Ph.D. candidate in Professor Zrenner's and Dr. Haq's lab at the Institute for Ophthalmic Research in Tuebingen. Her research focus is on the restoration of vision by electrical retinal implants.

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Validation of a Rabbit Model of Monocular Retinal Degeneration for Vision Restoration Applications

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2School of Optometry and Vision Science, UNSW, Sydney, New South Wales, Australia.

Purpose: We previously demonstrated that a unique feline model of retinal degeneration consisting of monocular photoreceptor degeneration and retinal remodelling can be generated through intravitreal injections of adenosine triphosphate (ATP) with no systemic effects. The binocularity of the feline visual system however means that cortical areas potentially remain unaltered following monocular retinal degeneration in this model through compensation by the contralateral healthy control eye. Thus, we determined whether ATP-induced retinal degeneration could be applied to a rabbit model which has little binocularity and would be preferred for the study of cortical responses to electrical stimulation of degenerated retina, as it may also mimic cortical changes.

Method: Normal-sighted Dutch rabbits (n=3) were examined for baseline characterisitcs using optical coherence tomography (OCT), fundus imaging, and ISCEV Standard full-field electroretinography (ERG). A single injection of 50 L ATP at a final vitreal concentration of 11 mM was administered intravitreally in one eye selected at random. Contralateral, control eyes were injected with equivolumes of saline. After two weeks, retinal structure (OCT) and function (ERG) were re-examined before the animals were euthanised and eyes enucleated, the retinae dissected, and cryosectioned for histology and immunocytochemistry.

Results: OCT imaging showed regions of variable retinal thickness in ATP injected eyes after two weeks. Adverse effects of intravitreal injections such as retinal detachment was not observed in any eyes. ERGs showed an average 61% reduction in a-wave (control eyes, 78.6±27.9 V; treated eyes, 27.2±18.4 V; p =0.1985) and average 53% reduction in oscillatory potential amplitudes (control eyes, 6.2±0.6 V; treated eyes, 2.8±0.8 V, p =0.0257). Histological analysis found significant retinal thinning in ATP treated eyes (mean thickness 108.1±2.7 m) versus control eyes (mean thickness 151.7±3.3 m; p < 0.01). Histology also revealed evidence of structural change consistent with retinal degeneration and remodelling such as rhodopsin redistribution into the nuclear layer and spherules, outer and inner segment loss and nuclear migration. There is also a loss of retinal lamination interspersed among stretches of seemingly healthy retina, consistent with evidence in human RP.

Conclusions: ATP delivered by an intravitreal injection can cause photoreceptor death and subsequent retinal remodelling in a rabbit model after two weeks. This unique animal model could be useful in the study of evoked cortical responses secondary to retinal degeneration and in vision restoration intervention experiments.

Biography: Hallur Reynisson completed his Master's in neurophysiology at the University of Iceland in 2018. His research characterized the electrophysiology of olfactory bulb projection neurons by patch clamping murine neuronal cultures. He was awarded the Jóhann Axelsson Prize for excellence amongst peers in physiology for his work. Prior to starting his Scientia Ph.D. project at University of New South Wales in 2020, he worked in industry at deCODE Genetics (2017-2020) and at Landspítali University Hospital (2014- 2017). He now aims to improve stimulation strategies of electrical neural implants to improve their usefulness and scope using in vivo electrophysiology.

Roksana Sadeghi, M.Sc.
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Number of Brightness Levels That Can Be Distinguished by Visual Prosthesis Users

Authors: R. Sadeghi, C. Bradley, M.P. Barry, A. Kartha, G. Dagnelie

Purpose: This study aims to develop a robust methodology to estimate the number of distinct brightness levels that can be distinguished by individuals implanted with a visual prosthesis.

Method: The amplitude thresholds of the electrodes of two Argus II users were estimated using a Bayesian adaptive method (Kontsevich et al. 1999). The amplitude threshold was defined to be the amplitude at which the detection rate was 50% in a yes/no experiment. For each electrode, the just-noticeable difference (JND) amplitude levels were estimated from different reference levels using a staircase method in a 2-alternative forced-choice paradigm, with the estimated thresholds being the lowest reference level for 22 electrodes in subject 1 and 21 electrodes in subject 2. A linear regression on the mean JNDs was used to identify the number of distinct visual perceptions that can be distinguished by the user.

Results: The slope of the best fitting line to the estimated log JND values was not significantly different from zero. Thus, consistent with Weber's law, our results show that for each electrode, the JND is proportional to the reference level. The range of perceived brightness levels was estimated to be between 2 and 18 levels per electrode. The distribution of the number of brightness levels in the two subjects is shown in Fig. 1. Linear regression on the mean JND values across all electrodes and reference amplitudes for each subject is shown in Fig. 2. These linear regressions can be used to predict the number of perceived brightness levels for other electrodes within the subjects' arrays once amplitude thresholds for the electrodes are estimated.

Conclusion: The number of distinct brightness levels estimated here for Argus II users can be obtained for other visual prostheses and is likely to vary by electrode and subject.

Biography: Roksana Sadeghi is a Ph.D. student in Biomedical Engineering at Johns Hopkins University. She's working with Dr. Gislin Dagnelie at Wilmer Eye Institute on visual prostheses. Her research interests are in translational neuro-engineering, including retinal and cortical visual implants. She holds M.Sc. in Biomedical Imaging at the University of California in San Francisco and finished her B.Sc. in Physics from the Sharif University of Technology in Iran, Tehran.

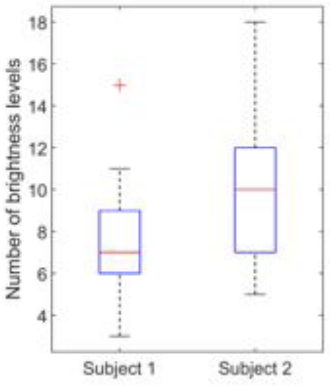


Fig.1. Number of brightness levels distribution.

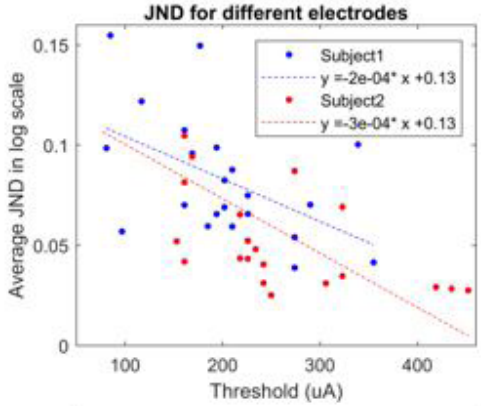
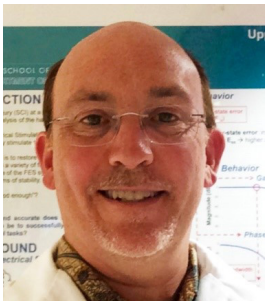


Fig.2. Linear regressions on mean JND values across all electrodes and thresholds.



Douglas Shire, Ph.D.
Bionic Eye Technologies
Ithaca, New York

Splaying Arrays for Stimulation of LGN and Cortex

Douglas Shire, Ph.D. and Marcus Gingerich, Ph.D., Bionic Eye Technologies, Inc.
Shelley Fried, Ph.D. and Sangbaek Ryu, Ph.D., Massachusetts General Hospital
Joseph F. Rizzo, MD, Massachusetts Eye and Ear Infirmary

Objective: This work is related to the efforts of the Bionic Eye team to develop a visual prosthesis to restore basic vision to the blind. A deep brain stimulation array has been developed that incorporates 64 individually addressable stimulation electrodes and can be inserted using a micro-drive into the lateral geniculate nucleus or the cortex. We have validated these designs by testing the device, both in vitro and in mouse models.

Methods: We have advanced our microfabrication methods over several device iterations to produce 64 channel, splaying implantable electrode arrays that were bonded to interface boards and in turn, to neurostimulation and recording apparatus. In addition, we adapted a split inserter from cardiac use to be able to deploy arrays in the deep brain and later withdraw the sheath, leaving the attached ribbon cables intact. An external insertion controller having both linear actuators and a microdrive head for visual prosthesis electrode insertion was designed and fabricated to operate the pre-loaded split inserters, and will also be presented. The arrays were formed into tines by reactive ion etching of plasma-deposited silicon carbide thin films and conventional photolithographic means. The resulting arrays are robust and are intended to fill a volume of the target tissue with electrodes at intervals, both by virtue of their spacing along the tines, and by the separation that those tines achieve as they are inserted into the target nucleus in the brain.

Results: Custom surgical insertion apparatus were used to deliver silicon carbide-based splaying electrodes to target tissue in mouse LGN. This array was used to both record visually evoked spikes from stimuli as they passed through the LGN tissue, and to electrically stimulate the same LGN region; the electrically evoked responses were recorded in V1 using a third party recording electrode (by Neuronexus). In vitro testing of the tine-based splaying electrode arrays and coated test substrates at 87C was also performed, and the films show excellent biostability and a projected lifetime of >10 years in biological saline. The 1000 square micron GSA electrodes were distributed along the length of 32 tines, with two electrodes per tine; the tine lengths were varied so as to access as much of the target tissue volume as possible upon insertion, due to the splaying characteristic. We will present electrochemical characterization results on the splaying electrodes before and after activation during slow cyclic voltammetry.

Conclusions: By employing electrodes intended for varied amounts of penetration depth within the target tissue and optimizing the splaying aspects of the arrays upon insertion using custom apparatus, we have been able to access, stimulate and record from mouse LGN, resulting in phosphenes that give rise to similar response characteristics in V1 compared to visually evoked responses. The results suggest that a high-density splaying array may be usable as the basis for an LGN based visual prosthesis to treat blindness from varied causes, including, for example, advanced glaucoma or diabetic retinopathy in addition to degenerative retinal diseases.

Biography: Dr. Doug Shire is the President and CTO of Bionic Eye Technologies, Inc., and the longtime Engineering Manager of the Boston Retinal Implant Project, founded by Dr. Joseph Rizzo and the late Dr. John Wyatt in the 1980s. That Project's mission has been to develop visual prostheses and related technology to aid the visually impaired, and Bionic Eye Technologies was formed to commercialize those technologies. Dr. Shire has published extensively on the applications of microfabrication technology to medical device manufacturing, with special emphasis on implantable electrodes.

Yoon-Kyu Song, Ph.D.
Seoul National University
Seoul, Korea

Imaging Action Potentials Across Retinal Ganglion Cells in Retinal Degenerative rd1 Blind Mice

Younginha Jung1, Sungmoo Lee2, Jun-Kyu Rhee2, Chae Eun Lee1, Bradley J. Baker2 and Yoon-Kyu Song1

1 Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea
2 Brain Science Institute, Korea Institute of Science and Technology, Seoul, South Korea

Purpose: Understanding retinal signaling network offers operational principles of functional ensembles which is crucial for developing visual prostheses. Over the past decades, neuronal activity has been measured through electrophysiology whereas the need to monitor population activity has led to advances in opto-physiology. This optical recording enables imaging retinal activity across the retina. To discover retinal network activity, this study utilized genetically encoded protein sensors, including voltage and calcium indicators.

Method: The mouse model with retinal degeneration one mutation (Pde6brd1) is intravitreally injected either with AAV-hSyn-Bongwoori-R3 or AAV-hSyn-GCaMP6f virus. A whole-mount retina is prepared for simultaneous electrophysiology and fluorescence imaging. For electrical stimulation with monophasic pulses, retinal ganglion cells are patched under current-clamp mode or Pt/Ir microelectrode is placed on retina tissue. Electrical and fluorescence signals from retinal ganglion cells are recorded and offline analyzed.

Results: At a cell level, the initiation and transmission process of action potentials is optically reported by voltage and calcium indicators. Bongwoori-R3 voltage signals are localized on cell body whereas GCaMP6f calcium signals are distributed over subcellular compartments. At a tissue level, effects of stimulus pulses on retinal cells are validated by comparing fluorescence changes. Voltage signals demonstrate that cathodic pulses elicit retinal responses at a distal area from the stimulus while anodic pulses at a proximal area.

Conclusion: This work attempts to apply voltage and calcium sensors on the photoreceptor-degenerated retina for optically imaging electrical activity. The voltage sensor, Bongwoori-R3, provides the means to track membrane voltage at multiple regions across retinal ganglion cells with spatial precision and temporal resolution. These results may lead us to the future work that new protein-based indicators, with sufficient signal quality and spatiotemporal resolution, will advance our understanding in retinal networks for artificial vision applications.

Biography: Yoon-Kyu Song received B.S. and M.S. degrees in electrical engineering from Seoul National University, Seoul, Korea, and his Ph.D. degree in electrical engineering from Brown University, Providence, Rhode Island. Following research faculty appointments at Brown, he is currently an associate professor at Seoul National University. His research interests include basic and applied semiconductor optoelectronics and neuroengineering.

Sophie Stürmer, M.Sc.
University of Tuebingen
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The Effect of Sustained Electrical Stimulation on the Retinal Gap-Junction-Coupled Lateral Pathways in the rd1 Mouse Model for Retinal Degeneration

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Purpose: In order to enhance the quality of artificial vision with electrical (e-) subretinal implants, the understanding of e-induced signal propagation through the degenerated retinal network is of great importance. As the retinal vertical synaptic signal transduction pathway has been investigated extensively, this study focuses on the lateral signal transmission through gap-junction (GJ) coupled networks. We investigated 1) the GJ-coupled cell networks of the photoreceptor-degenerated rd1 mouse retina (retinitis pigmentosa model) and 2) the impact of sustained e-subretinal stimulation (stim) on the GJ permeability.

Methods: The GJ coupling of the retinal networks was assessed by determining the GJ permeability via the tracer diffusion method. Therefore, acute retinal explants of the rd1 (P 21-26) were loaded with the GJ but not cell membrane permeant neurobiotin tracer by cutting an edge of the retina with a razor blade (Choi et al., 2012). In histological preparations, the analysis of tracer spread from its entry point at the cut through the GJ-coupled networks, was conducted by means of fluorescence microscopy. Sustained e-stim was applied subretinally (1 V for 1h at 1 Hz) using a single large electrode (5 mm), mimicking the integrated signal and surface of thousands of electrodes of an e-implant.

Results: 1) The rd1 retina displayed extensive intercellular coupling by open GJs. We identified three GJ-coupled networks: The horizontal, the amacrine and the ganglion cell network in the respective retinal layer. 2) The application of e-stim for durations of 1 h or longer diminished the spread of tracer through GJs in all cell layers, which was comparable to the pharmaceutical GJ inhibition by Carbenoxolone. The impact of the e-stim induced reduction of GJ permeability was related to the stim electrode position.

Conclusion: The GJ-coupled networks of the rd1 retina are not affected by the retinal degeneration and are functional (P 21-26). The modulation of the GJ permeability by sustained e-stim might be a direct or indirect effect (e.g., via neurotransmitter dopamine). These findings are of great relevance for the understanding of lateral signal spread induced by e-stim or via small molecules within the rd retina. Also, it is very likely that sustained e-stim alters spatial and temporal characteristics of the perceived visual sensation, indicating strong implications for the design of e-stim paradigms for implants.

Biography: Sophie Stürmer holds a B.S. in Psychology (University of Würzburg) and a M.S. in Neurobiology (University of Tübingen). She is currently a doctoral student in the Zrenner group at the Institute for Ophthalmic Research, University of Tübingen. Her research is focused on the effects of electrical and chemical stimulation on the degenerated retina.

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Bi-electrode Epiretinal Stimulation at Cellular Resolution for Axon Avoidance

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Subhasish Mitra1 & E.J. Chichilnisky2
1 Department of Electrical Engineering, Stanford University, Stanford CA, USA. 2 Departments of Neurosurgery, Ophthalmology, and Hansen Experimental Physics Laboratory, Stanford University, Stanford CA, USA. 3 AGH University of Science and Technology, Faculty of Physics and Applied Computer Science, 30-059 Krakow, Poland. 4Santa Cruz Institute for Particle Physics, University of California, Santa Cruz, CA, USA

Objective: Unwanted activation of axons and consequent arc-like phosphenes significantly degrade the quality of restored vision from epiretinal prostheses. Previous work has suggested that axon activation can be avoided with spatial stimulation strategies that minimize the second spatial derivative of the extracellular voltage induced along the axon. However these findings have not been verified experimentally at cellular resolution. Here, we use large-scale multi-electrode recording and stimulation in an isolated macaque retina, with a biophysically guided bi-electrode stimulation strategy, to test axon avoidance at cellular resolution.

Methods: A 512-electrode system (10 m diameter; 60 m pitch) was used to stimulate and record from RGCs in isolated macaque retina. Responses to visual stimulation were used to determine the cell type and electrical signatures of spiking RGCs. Electrical stimulation consisted of charge balanced, tri-phasic current pulses supplied at one or two electrodes simultaneously while recording from all electrodes. The response of ON and OFF parasol RGCs to electrical stimulation was analyzed using supervised template matching and summarized by the threshold current that yielded 50% activation probability. Stimulation of a target soma and non-target axon with one electrode was compared to stimulation that also included equal and opposite current passed through a second electrode on the opposite side of the axon. The stimulating electrodes were chosen to minimize the second spatial derivative of the extracellular voltage along the axon, a quantity that drives extracellular axonal activation.

Results: Bi-electrode stimulation increased the thresholds of non-target axons (consistent with previous simulation studies) and decreased the thresholds of target somas (potentially explained by increased electric field magnitude from the second active electrode), thus favoring somatic activation. Selectivity, defined as the ratio of axon threshold to soma threshold, was higher using bi-electrode stimulation, further confirming more effective targeting of somas over axons. These findings were consistent for 48 cell-electrode pairs analyzed across three retinas.

Conclusions: Biophysically guided bi-electrode stimulation enhanced the selectivity of RGC somatic activation over axonal activation at cellular resolution, demonstrating a stimulation strategy that can reduce axonal activation for high-fidelity artificial vision.

Biography: Raman completed his B.S. with Honors ('18) at The Ohio State University in Electrical Engineering where he worked on bio-medical sensing technologies in the Wearable and Implantable Technologies Lab. He is currently an E.E. Ph.D. Candidate at Stanford and a recipient of the Stanford Graduate Fellowship. He is working on the Stanford Artificial Retina Project with a focus on designing, simulating, and testing novel multielectrode electrical stimulation patterns for brain-machine interfaces.

Marcos Villamarin-Ortiz, M.Sc.
University Miguel Hernandez
Elche, Spain

Enhancing the Biocompatibility of Intracortical Microelectrodes by Controlled Release of Dexamethasone Using Nanostructured Lipid Carriers

Villamarín-Ortiz, Marcos Adrián; Lafuente, Markel; Pedraz, José Luis; Soto-Sánchez, Cristina; Fernández, Eduardo

Purpose: Cortical protheses are a subgroup of visual neuroprostheses capable of evoking visual percepts in profoundly blind people through direct electrical stimulation of the occipital cortex. However, the implantation of any intracortical microelectrode induces biological responses characterized by small microhemorrhages and a certain amount of local tissue damage around the electrodes that may impact the stability, performance, and viability of the microelectrodes. A significant challenge here is to reduce the neuroinflammatory response.

Methods: We have developed a novel film sheet composed by nanostructured lipid nanocarriers (NLCs) loaded with dexamethasone (Dex) to improve long-term biocompatibility of cortical implants. A 4-shaft microelectrode array was inserted in the visual cortex of 14 rats following standard procedures. After successful implantation the microelectrodes were covered by a piece of the new film cut to the size of the microelectrode array. Astrocytes, microglial cells and neurons surrounding microelectrodes were investigated by immunohistochemistry techniques 14 days post/surgery. Integrated density (Int) of relative fluorescence units (RFU) and phenotypic state of microglia were quantified in regions nearby the probe-tissue interface.

Results: GFAP staining for reactive astrocytes was significantly lower in the group of animals treated with the novel film. The average glial scar width was reduced from 25 m ± 5 in the non-treated groups to 9 m ± 2 in the treated group. The Iba1 staining did not show significant variations in the number of microglial cells close to microelectrodes shanks between both groups, but the pattern of ramifications of microglial cells in the treated group was most similar to the resting state of microglia. Furthermore, neurons were closer to the implanted probes in the treated group (10 m ± 3 surrounding the electrodes) compared with the non-treated groups (21 m ± 6).

Conclusion: Our results suggest that the novel film sheet composed by nanostructured lipid nanocarriers (NLCs) loaded with dexamethasone (Dex) effectively prevents the reactive responses around neural probes. Although more studies are still needed, local and controlled release of bioactive molecules close to implanted neural probes may represent a promising approach to control the biological responses and improve long-term biotolerability of intracortical microelectrodes.

Biography: Marcos Adrián Villamarin Ortiz is a research personnel and doctoral candidate at the Bioengineering Institute of the Miguel Hernández University of Elche, Spain. In 2016, Marcos received his Bachelor's as Biotechnology Engineer from his hometown university in Ecuador, Salesian Polytechnic University financed by a private-public fellowship, then he earned the Carolina's Foundation (FC) fellowship to complete his Master's degree in Biotechnology and Bioengineering at the Miguel Hernandez University in Spain. Before he started his Ph.D., he worked as assistant professor at the Private Technical University of Loja in Ecuador. At present, Marcos's doctoral research is supported by the Santiago Grisolia fellowship from the Generalitat Valenciana-Spain. Marcos's research focuses on the acute and long-term biocompatibility of brain microelectrode implants, using novel non-viral vectors for drug-gene therapy, and the brain plasticity as the ability of neural networks to learn and reorganize itself.

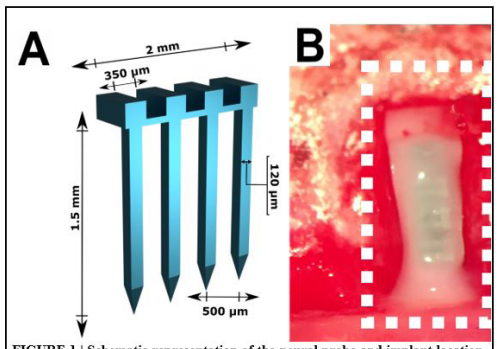
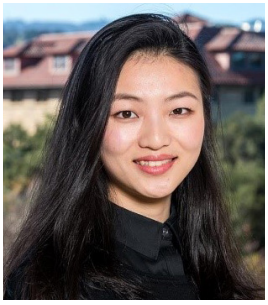


FIGURE 1 | Schematic representation of the neural probe and implant location. (A) 3D represenentation of the intracortical microelectrode array. (B) NLCs+Dex film covering the implanted electrode array in the rat brain cortex.

FIGURE 1 | Schematic representation of the neural probe and implant location. (A) 3D represenentation of the intracortical microelectrode array. (B) NLCs+Dex film covering the implanted electrode array in the rat brain cortex.



Bingyi Wang, B.A.
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Subretinal Planar and 3D Photovoltaic Arrays Enable Prosthetic Vision Matching the Natural Acuity of 27μm in Rats

Bing-Yi Wang1, Mohajeet Bhuckory2, Zhijie Charles Chen4, Tiffany Huang4, Andrew Shin5, Ludwig Galambos3, Valentina Zuckerman3, Elton Ho1, Keith Mathieson6, Theodore Kamins4, and Daniel Palanker2,3

1Physics 2Ophthalmology, 3Hansen Experimental Physics Laboratory, 4Electrical Engineering, 5Material Science, Stanford University, Stanford, CA, USA. 6Institute of Photonics, Dept. of Physics, University of Strathclyde, Glasgow, UK

Purpose: High visual acuity in prosthetic vision requires effective stimulation by small pixels with little crosstalk. Planar bipolar pixels have shallow penetration of the electric field, leading to a retinal stimulation threshold exceeding the safe charge injection limit for pixels under 40μm. To bypass such limitation, we developed planar and 3D monopolar arrays with deep-penetrating field and investigated their stimulation threshold and visual acuity in vivo.

Methods: The 1.5 mm-wide hexagonal arrays of photovoltaic pixel of 20 or 40μm in width were produced with and without the 25μm-tall walls surrounding each pixel, with a common return ring at the edge of the device. To reduce the crosstalk, some pixels were converted into transient local returns by spatiotemporal modulation of their conductivity. Following subretinal implantation in rats with a degenerate retina (RCS), visually evoked potentials (VEP) were recorded in response to pulsed NIR (880nm) activation of the implants. The full-field stimulation threshold was measured with 10ms pulses at 2Hz, while acuity was assessed using gratings alternating at 2Hz, under 4ms stimulation applied either at 64Hz or multiplexed into 4 sub-frames at 256Hz.

Results: The full-field stimulation threshold was 0.057 ± 0.029mW/mm2, corresponding to a current density of 0.092mA/mm2 on the active electrodes, independent of pixel size and presence of the walls. This is nearly 30 times lower than with bipolar pixels of 40μm in size. On the day of implantation, VEP amplitude typically exceeds 100μV, but it dropped to tens of μV one week later, and gradually recovered back to the initial level within about 15 weeks post-op. With 20μm pixels, planar and 3D, grating acuity (about 27μm) matched the natural resolution observed in wild-type controls.

Conclusions: Subretinal photovoltaic arrays with nearly-vertical electric field provided stimulation thresholds independent of the pixel size, and much lower than those with bipolar pixels. Using optical spatiotemporal modulation of the photodiode conductivity, any subset of pixels can be converted into transient local returns, thereby providing field confinement necessary for high resolution. Presence of the vertical walls did not negatively affect the retinal excitability, paving the way to honeycomb implants with local returns. We hope that in human patients, arrays composed of such 20μm pixels will enable prosthetic vision with acuity as high as 20/80.

Biography: Bingyi Wang is a Ph.D. candidate in Physics at Stanford University, where she develops high acuity subretinal prosthesis in Prof. Daniel Palanker's group. She focuses on optimizing photovoltaic substitute for lost photoreceptors to enable prosthetic vision with high visual acuity, paving the way for meaningful sight restoration in AMD patients. In addition to her scientific endeavor, she is a Knight-Hennessy scholar and completed the Ignite program in innovation and entrepreneurship at Stanford Graduate School of Business.

Aiwen Xu, B.S.
University of California, Santa Barbara
Santa Barbara, California

Deep Learning–based Scene Simplification Can Improve Prosthetic Vision Quality: A Study With Simulated Prosthetic Vision

Aiwen Xu, Nicole Han, Sudhanshu Srivastava, Devi Klein, Michael Beyeler

Purpose: The quality of current prosthetic vision is rudimentary but may possibly be improved with image preprocessing. In this study, we combined various computer vision models with a neurobiologically inspired, psychophysically validated computational model of the retina (Beyeler et al., 2019) to generate simulated prosthetic vision (SPV), and systematically evaluated the ability of these algorithms to support scene understanding (Fig. 1). Whereas previous studies assumed that phosphenes are isolated, focal spots of light, here we assessed perceptual performance across a wide range of common phosphene shapes as well as electrode grid sizes.

Methods: 45 sighted subjects (31 females, 14 males) acted as virtual patients by watching SPV videos depicting 16 different outdoors scenes. Subjects were asked to identify if there were people and/or cars in the scene. Perceptual performance was measured as a function of four deep learning-based scene simplification strategies (highlighting visually salient information, highlighting closer pixels, segmenting relevant objects, and a combination of all three), three retinal implant resolutions (8x8, 16x16, 32x32), and nine different combinations of phosphene size and elongation.

Results: Subjects were best at identifying people and cars with the segmentation algorithm (d'=1.13, sd=1.02) compared to saliency (d'=0.07, sd=.66, p<0.001), depth (d'=0.29, sd=0.77, p<0.001), and combination (d'=1.01, sd=0.91, p<0.05). As expected, performance improved as the number of electrodes in the array was increased from 8x8 (d'=0.46, sd=0.87) to 16x16 (d'=0.72, sd=0.93, p<0.001), but not when further increased to 32x32 (d'=0.72, sd=1.06). Performance with the smaller phosphene size (100 m) was significantly better (d'=0.81, sd=1.02) than larger phosphene sizes 300 m (d'=0.6, sd=0.89, p<0.05) and 500 m (d'=0.52, sd=0.96, p<0.05).

Conclusion: We identified object segmentation as the most promising image processing strategy to support outdoor scene understanding of virtual patients. However, perceptual performance was drastically affected by phosphene size. This finding highlights the importance of accounting for realistic phosphene shape when making predictions about prosthetic performance.

Biography: Aiwen Xu is a Ph.D. candidate in Computer Science from the Bionic Vision Lab at University of California, Santa Barbara. Prior to UC Santa Barbara, she received a B.S. in Computer Science and a B.S. in Mathematics from New York University, Shanghai. Her research interest is in utilizing mathematical modeling and machine learning techniques to improve bionic vision.

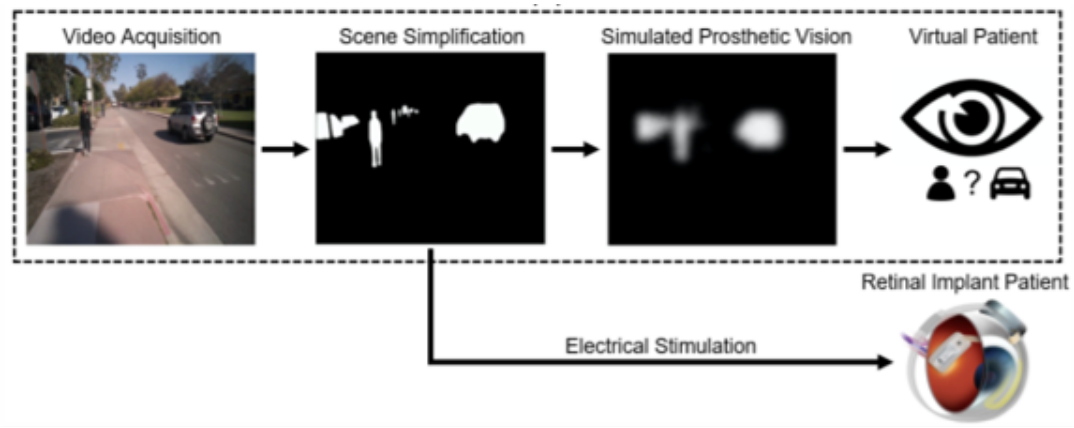

Figure 1: To create meaningful artificial vision, we explored deep learning–based scene simplification as a preprocessing strategy for retinal implants.

Hongze Zhong, M.Sc.
Newcastle University
Newcastle, United Kingdom

Thermophysical Optimization of the Optogenetic Visual Prosthesis

Hongze Zhong, Patrick Degennar, Neuroprosthetics Lab, Newcastle University

The Newcastle Optogenetic Visual Cortical Prosthesis project aims to create an optogenetic version of a cortical prosthesis. This will involve inserting penetrating light emissive probes into the tissue – See Figure 1(a). However, no LED has 100% electrical to optical conversion efficiency. In fact, most micro-LEDs have published efficiencies of just a few percent compared to commercial mini-LEDs with around 30% efficiency. In both cases, the waste energy is expressed as heat. Moreover, the regulatory limit for any probe surface in tissue is $T \leq 2$ above ambient (i.e. $T \leq 39$). Although acute rises higher than this is unlikely to cause ill-effect. Long term chronic use at elevated temperatures could cause cell damage. Currently, our probes are relatively large – limited primarily by the size of the mini-LEDs. But these will reduce in size, and more efficient micro-LEDs will become available. As such, the question arises as to how the thermal effects above will scale as probes become larger and the number of LEDs turned on increases?

Based on the above, the aim of this work is to focus on the thermal effects (Figure 1(b)) for different probe dimension. In this study, we have used finite element modelling to explore how this scaling for different probe dimensions and geometries for given thermal pulse regimes (depending on LED efficiency). We will present the outcome of this effort to try to draw a general operational window for optogenetic probes in the brain from a thermal perspective.

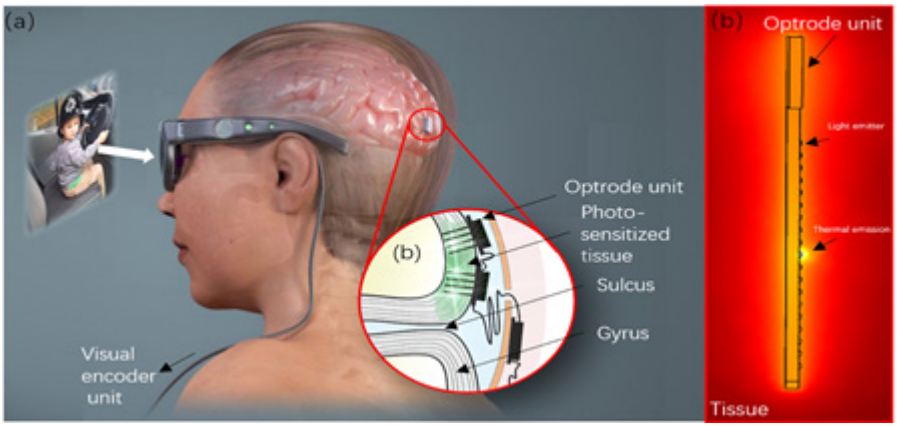

Figure1 (a) The Newcastle Optogenetic Visual Cortical Prosthesis project. (b) Using the finite element method can provide an accurate thermal distribution simulation.

Biography: Hongze Zhong received his M.Sc. degree from Newcastle University, UK, in 2019. He is currently a Ph.D. student at Newcastle University under supervision of Dr. Patrick Degenaar, with focus on simulation and fabrication of implantable devices.

Muru Zhou, B.S.
University of Michigan
Ann Arbor, Michigan

Shape Changing Polymer Bilayer for Implanted Epiretinal Flexible Electronics

Muru Zhou, Do Hyun Kang, Jinsang Kim, James Weiland

Purpose: Hydrogel/elastomer bilayers have a tunable shape morphing ability, flexibility and biocompatibility. However, there are few studies of implanted electronics using a hydrogel/elastomer bilayer. This project studies the potential to use hydrogel/elastomer hybrid as the substrate for flexible epiretinal electronics.

Method: A bilayer system with polydimethylsiloxane (PDMS)/polyacrylamide (PAAm) was fabricated. While PDMS works as the passive layer defining the motion of hydrogel, the PAAm active layer can respond to water and change the shape of the bilayer by swelling and deswelling [1]. Metal conductive lines and electrodes were fabricated on PDMS [2]. Currently, the fabrication was still under continuous optimization.

Results: Benzophenone was used to bond the wet PAAm hydrogel and PDMS with good reliability and allowed the bilayer to remain integral after 72 hours in water [3]. The curvature of the bilayer is tunable by controlling the initial concentration of monomer and crosslinkers, and the thickness ratio between the hydrogel and the elastomer layer. Initial results showed that with a high initial monomer concentration at 20 wt%, the PAAm hydrogel had 1) a decreased expansion strain, 2) an increased Young's modulus when hydrated, and 3) an increased thickness when fully dried (Figure 1). A flower-shaped bilayer was fabricated as a potential configuration of the final device (Figure 2). A bimetallic strip model developed by Timoshenko [4] was used and showed that the predicted and experimentally obtained curvature follow a similar trend. Initial electrode fabrication showed successful deposition of a Cr/Au metal layer on PDMS. Opening the electrode site on the top PDMS encapsulation layer using wet etching is still under development.

Discussion: The hydrogel/elastomer system has the potential to be a substrate for a retinal stimulating array to provide a way to resolve the conflict between maximizing the size of the electronics and minimizing the surgical trauma. Optimized fabrication of metal conductive lines and electrodes on the novel substrate is still under exploration.

Biography: Muru Zhou is a 5th year Ph.D. student in the Macromolecular Science and Engineering Program at University of Michigan, Ann Arbor. She obtained her B.S. from Pharmaceutical Science at Fudan University, China. Her current research focuses on developing shape-morphable and flexible epiretinal prostheses using hydrogel/elastomer bilayer.

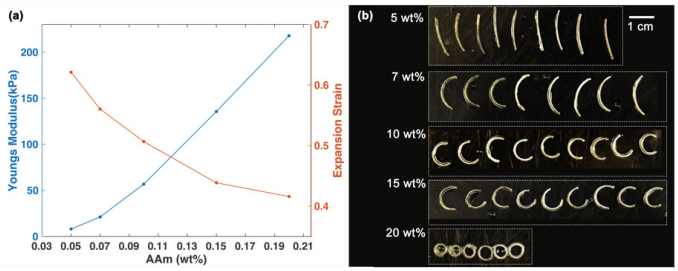

Figure 1: Characterizations of hydrogels and curvature measurement of bilayer strips. (a) Young's modulus and expansion strain of hydrated hydrogels with different AAm initial concentrations. (b) Hydrated bilayer strips (17 mm x 2.5 mm (length x width) with different AAm wt%.

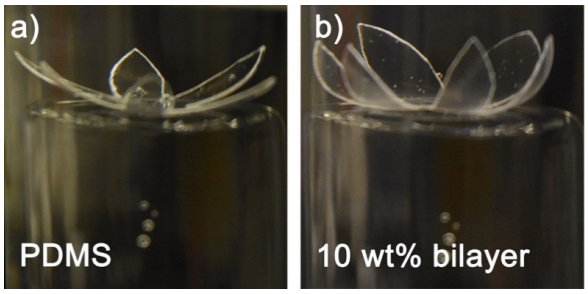

Figure 2: (a) PDMS without PAAm layer. (b) Bilayer samples with 10 wt% initial monomer concentration.

The Eye and The Chip
Bartimaeus Award Recipients 2004-2019

The Bartimaeus Award is presented to an investigator who has distinguished himself or herself by prolonged substantial contributions to the progress in this field of The Eye and The Chip.

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Co-Founder, Boston Retinal Implant Project
Massachusetts Eye and Ear Infirmary
David G. Cogan Professor of Ophthalmology
in the field of Neuro-Ophthalmology,
Director of the Neuro-Ophthalmology Service
Harvard Medical School
Massachusetts Eye & Ear
Chair of Alumni Reunion
Boston, Mass.

Eberhart Zrenner, M.D. (2006)
Chair Professor of Ophthalmology
Center for Ophthalmology
Institute for Ophthalmic Research
University of Tuebingen
Tübingen, Germany

Richard Normann, Ph.D. (2008)
Distinguished Professor of Bioengineering
and Ophthalmology
Moran Eye Center, University of Utah
Salt Lake City, Utah

Robert Greenberg, M.D., Ph.D. (2010)
President & CEO
Second Sight Medical Products, Inc.
Sylmar, Calif.

Mark Humayun, M.D., Ph.D. (2010)
Professor of Ophthalmology
Biomedical Engineering, Cell and Neurobiology
Keck School of Medicine of the
University of Southern California
Associate Director of Research, Doheny Eye Institute
Los Angeles, Calif.

Nigel Lovell, Ph.D. (2012)
Professor
University of South Wales
Sydney, Australia

Gregg Suaning, Ph.D. (2012)
Associate Professor
University of South Wales
Sydney, Australia

James Weiland, Ph.D. (2014)
Professor of Ophthalmology &
Biomedical Engineering
University of Southern California
Los Angeles, CA

Gislin Dagnelie, Ph.D. (2016)
Johns Hopkins University School of Medicine
JHU Lions Vision Center
Baltimore, MD

Shelly Fried, Ph.D. (2017)
Associate Professor
Department of Neurosurgery
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

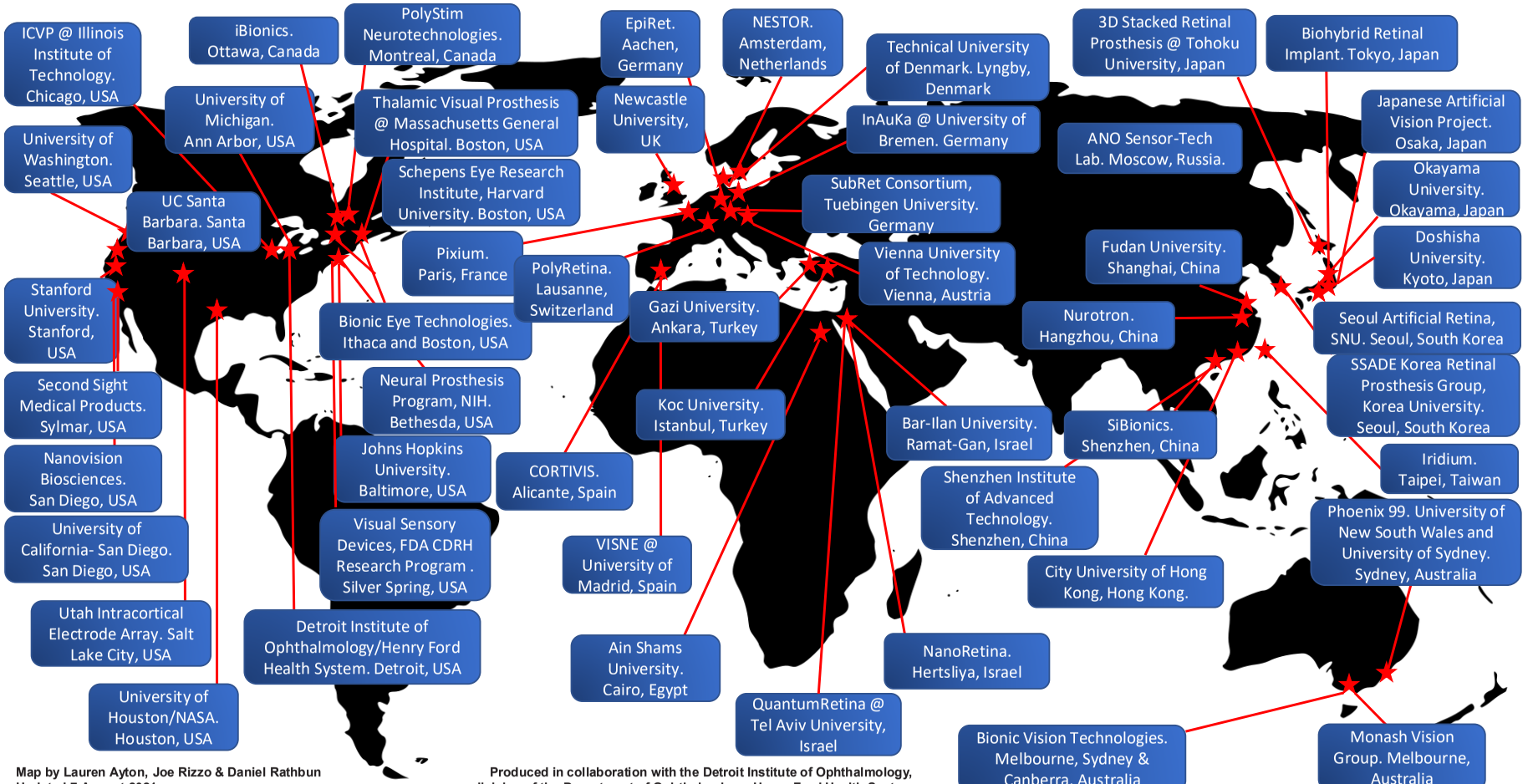
Daniel Palanker, Ph.D. (2019)
Professor of Ophthalmology
Director, Hansen Experimental Physics Lab
Stanford University
Stanford, California

Daniel Palanker, Ph.D. accepting the Bartimaeus Award from Joseph Rizzo, M.D. at the 2019 The Eye and The Chip Bartimaeus Award Dinner.

Titles listed are at the time of receiving the Bartimaeus Award

NOTES:

CURRENTLY ACTIVE INTERNATIONAL VISION PROSTHESIS GROUPS



Map by Lauren Ayton, Joe Rizzo & Daniel Rathbun
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