The Eye and The Chip
World Congress on Artificial Vision

THE 11TH WORLD CONGRESS

On the Relationship Between Neurobiology and Nano-Electronics Focusing on Artificial Vision

November 10-12, 2019
The Henry, An Autograph Collection Hotel

Henry Ford Health System

DEPARTMENT OF OPHTHALMOLOGY

Detroit Institute of Ophthalmology

Henry Ford Health System

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Detroit Institute of Ophthalmology

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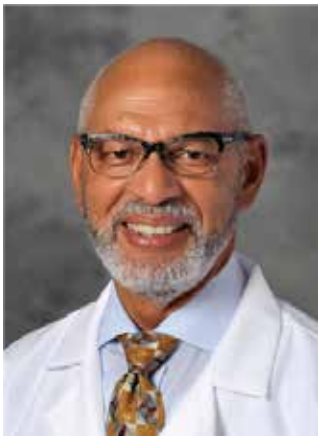


Welcome

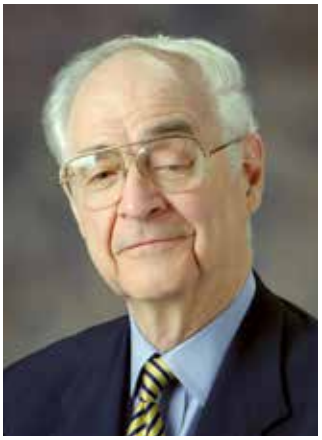
On behalf of the Henry Ford Health System and the Department of Ophthalmology, welcome to The Eye and the Chip 2019 World Research Congress. The World Congress planning team, have brought together the world's foremost experts on the development of neuro-prosthesis for vision restoration for patients who are blind or severely vision impaired. This year our focus will be:

- Identifying areas of progress in the marriage of neurobiology and nanotechnology that will allow devices to be placed in the eye or the brain to restore vision to those who are now blind.
- A collegial interchange that will help to achieve collaborative relationships between programs in Europe, America, Asia and Australia
- Identifying advances and challenges remaining in the global pursuit of true artificial vision
- Identifying outcomes of device implantation where it is occurring
- Identifying progress in the USFDA approval of visual neuro-prosthetic device implantation in humans.

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 traveled from near and far. 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
The McCole Chair
Department of Ophthalmology
Henry Ford Health System



Thoughts on The Eye and The Chip

So… why, with commercial endeavors here in the US and in Europe interrupted, are hopes not quashed for a visual nano-electronic device?

Why, too, if the retinal approach, among the four avenues for artificial vision under study, is challenged has there been a very significant increase in interest?

And indeed, hopes do remain robust and interest is increasing —- one need only consider that:

> The Eye and The Chip 2019 has entries — platform and poster — in numbers far exceeding any year in the past. And that there are efforts from dozens more initiatives around the world than ever in the past.

Why? Because there are glimmers of evidence that the approach works. There has been 'proof of principle'. At The Eye and The Chip 2017 we noted that, to increase image resolution to the point where the recipient patient was pleased with the endeavor, there needed to be breakthroughs in the electronic or materials world as well as a better understanding of the brain (After all, isn't the retina simply a piece of the brain set out on a stalk?).

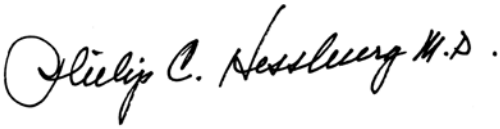
There have been brain breakthroughs that are simply staggering in their significance. In my residency days in ophthalmology we talked of retinal ganglion cells. Now we know there are several dozen varieties of RGCs each with different neural responsibilities. A device must unwrap that cocoon.

And breakthroughs abound in our cell phones and in our neuro-electronics. Recently we talked of micro-electrodes 'thinner than a human hair'. Now investigators are working with micro electrodes which make those electrodes look medieval and enormous.*

As work proceeds among groups on virtually every continent, because of HOVER** we know that we will approach results, and an understanding of how those results were obtained, in a manner satisfying to us as ethical scientists. And we will be using a document cooked up out of our own body of workers, without government dictates of any kind, that is, I believe, absolutely unique in the field of human clinical research.

So… Be not afraid. We are a blessed endeavor. All indications are that those gathered in this room for three days will ultimately, in a very patient satisfying way, lift a portion of the burden of those who suffer loss of vision.

Godspeed!



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Medical Director, Detroit Institute of Ophthalmology
Senior Staff Ophthalmologist, Henry Ford Health System

* An integrated brain-machine interface platform with thousands of channels Elon Musk Neuralink, 7 18 2019 doi: https://doi.org/10.1101/703801

** HOVER "Harmonization of Outcomes and Vision Endpoints in Vision Restoration"

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.

For more than 44 years, that's been the mission of the Detroit Institute of Ophthalmology, the research education arm of the Henry Ford Department of Ophthalmology (DIO). 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 each year 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 & The Auto, and The Eye and The Chip. Find more information at: www.henryford.com/heeyeandthechip

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 businesses. 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.

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HEARING IMPAIRED STATEMENT: Henry Ford Health System is committed to ensuring that our guests who are deaf or hard-of-hearing have equal access to all the services provided at our facilities. We provide at no cost the appropriate auxiliary aids and services. To request an assistive listening device or service, please email Tina Miller at cmille26@hfhs.org or call (313) 916-8354.

PROGRAM SCHEDULE

SUNDAY, NOVEMBER 10, 2019

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)

7:00 - 8:00 a.m. **CONTINENTAL BREAKFAST**

7:45 - 7:55 am WELCOME & INTRODUCTION
Paul A. Edwards, M.D. Chair, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

7:55 - 8:00 am **HOUSEKEEPING ANNOUNCEMENTS**
David J. Goldman, M.D., M.B.A., Associate Medical Director, Detroit Institute of Ophthalmology, Director of Residency Program, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session One: Current Clinical Trials, Patient Outcomes and Experiences
MODERATOR – Lauren Ayton, Ph.D., University of Melbourne, Melbourne, Australia

8:00 - 8:30 a.m. Orion Visual Cortical Prosthesis System: One-Year Clinical Trial Results
Jessy Dorn, Ph.D., Second Sight, Sylmar, California

8:30 - 9:00 a.m. The Bionic Vision Technologies Suprachoroidal Retinal Prosthesis: Interim Clinical Results
Matthew Petoe, Ph.D., Bionic Vision Technologies, Melbourne, Australia

9:00 - 9:30 a.m. Photovoltaic Restoration of Sight in Age-related Macular Degeneration: One-Year Clinical Results
Daniel Palanker, Ph.D., Stanford University, Stanford, California
Yannick Le Mer, M.D., Pixium-Vision, Paris, France

9:30 - 10:00 a.m. **BREAK**

10:00 - 10:30 a.m. Towards a Cortical Visual Neuroprosthesis for the Blind: Preliminary Results in a Human
Eduardo Fernandez, M.D., Ph.D., University of Miguel Hernandez, Elche, Spain

10:30 - 11:00 a.m. The Perceptual Experience of Artificial Vision: Qualitative Reports of Epiretinal Implant Users
Cordelia Erickson-Davis, M.D., Stanford University
Helma Korzybska, Ph.D. Candidate, LESC, Paris Nanterre University, France

11:00 - 11:30 a.m. **GROUP DISCUSSION**

11:30 - 12:30 p.m. **LUNCH**

SUNDAY, NOVEMBER 10, 2019

Session Two: Improving Patient Outcomes and Experiences with Current Generation Devices
MODERATOR – Gislin Dagnelie, Ph.D., Johns Hopkins Hospital, Baltimore, Maryland

12:30 - 1:00 p.m. Educational Techniques to Enhance Comprehension of Complex Information
Frank Lane, Ph.D., Illinois Institute of Technology, Chicago, Illinois

1:00 - 2:00 p.m. PANEL – HOVER Update
Members: Lauren Ayton, Ph.D., University of Melbourne, Australia
Joseph Rizzo, M.D., Harvard Medical School, Boston,Massachusetts

2:00 – 2:30 p.m. Novel Vision Processing Method Facilitates Color Contrast Object Detection in Participants Implanted with a Suprachoroidal Retinal Prosthesis
Nick Barnes, Ph.D., Bionic Vision Technologies, Melbourne, Australia

2:30 - 3:00 p.m. The Color Option
Vernon Towle, Ph.D., Illinois Institute of Technology, Chicago, Illinois

3:00 - 3:30 p.m. **BREAK**

3:30 - 4:00 p.m. Temporal Dithering of Epiretinal Stimulation to Optimize Artificial Vision
Nishal Shah, M.Sc., Stanford University, Stanford, California

4:00 - 4:30 p.m. Applications of Deep Learning AI to Neural Signal Analysis, Sight Perception, Device Design and Neural Stimulation Patterning
Greg Auner, Ph.D. Wayne State University, Henry Ford Health System, Detroit, Michigan

4:30 - 5:00 p.m. Pulse Trains to Percepts: The Challenge of Creating a Perceptually Intelligible World Based on Cortical Stimulation of Early Visual Areas
Ione Fine, Ph.D., University of Washington, Seattle, Washington

5:00 – 5:30 p.m. **GROUP DISCUSSION**

6:00 - 9:00 p.m. **BARTIMAEUS DINNER – Reservations required.**
Contact Roseanne Horne - Rhorne1@hfhs.org or 313-936-1968

MONDAY, NOVEMBER 11, 2019

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)

7:00 - 8:00 a.m. **CONTINENTAL BREAKFAST**

7:45 – 7:55 a.m. **WELCOME & INTRODUCTION**
Philip C. Hessburg, M.D., Medical Director, Detroit Institute of Ophthalmology, Henry Ford Health System, Grosse Pointe Park, Michigan

7:55 – 8:00 a.m. **HOUSEKEEPING ANNOUNCEMENTS**
David Goldman, M.D., M.B.A., Associate Medical Director, Detroit Insitute of Ophthalmology, Director of Residency Program, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session Three: Next Generation Devices
MODERATOR – James Weiland, Ph.D. University of Michigan, Ann Arbor, Michigan

8:00 - 8:30 a.m. Intracortical Visual Prosthesis (ICVP): Progress Towards the Clinical Trial
Philip Troyk, Ph.D., Illinois Institute of Technology, Chicago, Illinois

8:30 - 9:00 a.m. OptoViS: Optogenetic Visual Cortical Prosthesis
Patrick Degenaar, Ph.D., Newcastle University, Newcastle, United Kingdom

9:00 - 9:30 a.m. Towards the Development of a Micro-coil Based Cortical Visual Prosthesis
Shelley Fried, Ph.D., Massachusetts General Hospital, Boston, Massachusetts

9:30 - 10:00 a.m. **BREAK**

10:00 - 10:30 a.m. The High Resolution Imaging Retinal Prosthesis (HARP4k) -- Status Update on Tissue Tolerance
Long-Sheng Fan, Ph.D., Iridium Medical Technology Co., Ltd., Taiwan, Republic of China

10:30 - 11:00 a.m. Real-time Beam Trajectory Control for Fully Wireless Optically Powered Epiretinal Prostheses
Ross Cheriton, Ph.D., Australia – Canada Bionic Vision Collaboration, Ontario, Canada

11:00 -11:30 a.m. **GROUP DISCUSSION**

11:30 - 12:30 p.m. **LUNCH**

MONDAY, NOVEMBER 11, 2019

Session Four: Next Generation Devices and Materials
MODERATOR - Daniel Rathbun, Ph.D., Henry Ford Health System Bionics and Vision Lab, Detroit, MI

12:30 - 1:00 p.m. A Silk Fibroin Biohybrid Thalamic Visual Neuroprosthesis. First Steps for the Development of the Biohybrid Retina
Fivos Panetsos, Ph.D., VISNE, Madrid, Spain

1:00 – 2:00 p.m. PANEL – Cortical Prostheses
Members: Avi Caspi, Ph.D., Jerusalem College of Technology, Jerusalem, Israel
Patrick Degenaar, Ph.D., University of Newcastle, Newcastle, United Kingdom
Eduardo Fernandez, M.D., Ph.D., University of Miguel Hernandez, Elche, Spain
Shelley Fried, Ph.D., Massachusetts General Hospital, Harvard Medical School, Boston Massachusetts
Phil Troyk, Ph.D., Illinois Institute of Technology, Chicago, Illinois

2:00 - 2:30 p.m. The Diamond Eye: Architecture and Reduction to Practice
Steven Prawer, Ph.D., Australia-Canada Bionic Vision Consortium, Victoria, Australia

2:30 - 3:00 p.m. A Fully Wireless 288 Electrodes Retinal Implant with an Optical Data and Power Link with Ultrananocrystaline Diamond Electrodes
William LeMaire, Ph.D., Canada-Australia Bionic Vision Consortium, Sherbrooke, Canada

3:00 - 3:30 p.m. **BREAK**

3:30 - 4:00 p.m. In-vitro Study and Capacitive Behavior of Photovoltaic, Subretinal Implant with 3D Carbon Electrodes
Rasmus Davidsen-Schmidt, Ph.D., Technical Univerity of Denmark, Lyngby, Denmark

4:00 - 4:30 p.m. Nanowire Arrays Restore Vision in Blind Mice
Jiayi Zhang, Ph.D., Fudan University, Shanghai, China

4:30 – 5:00 p.m. Expanding the Restorative Capacity of Visual Prostheses Beyond Retinal Diseases: Neurofibromatosis as an Iconic Example
Steven Stasheff, M.D., Ph.D., National Institute of Health National Eye Institute, Bethesda, Maryland

5:00 – 5:30 p.m. **GROUP DISCUSSION**

5:30 –7:30 p.m. **POSTER PRESENTATIONS AND COCKTAIL HOUR**

TUESDAY, NOVEMBER 12, 2019

(Presentations are 20-minutes long, plus a 10-minute Q & A – Challenge period)

7:00-8:00 a.m. **CONTINENTAL BREAKFAST**

7:55 a.m. **HOUSEKEEPING ANNOUNCEMENTS**
David J. Goldman, M.D., M.B.A., Associate Medical Director, Detroit Insitute of Ophthalmology, Director of Residency Program, Department of Ophthalmology, Henry Ford Health System, Detroit, Michigan

Session Five: Understanding the Degenerate Retina and Visual Pathway
MODERATOR- Eberhart Zrenner, M.D., University of Tuebingen, Tuebingen, Germany

8:00 - 8:30 a.m. Electrical Response Clustering of Mouse Retinal Ganglion Cells
Daniel Rathbun, Ph.D., Henry Ford Bionics and Vision Lab, Detroit, Michigan

8:30 - 9:00 a.m. Experimentally Constrained Predictions of the Efficacy of a Global Activity Shaping Strategy
Martin Spencer, Ph.D., Bionic Vision Technologies, Melbourne, Australia

9:00 - 9:30 a.m. Replicating a More Physiological Retinal Neural Code Using High-Rate Electrical Stimulation
Tianruo Guo, Ph.D., University of New South Wales, Sydney, Australia

9:30 - 10:00 a.m. **BREAK**

10:00 - 10:30 a.m. Real Time Imaging of the Microglia Response to Electrical Overstimulation of the Retina Under Epiretinal Stimulus Electrodes
Ethan Cohen, Ph.D., US FDA, Silver Spring, Maryland

10:30 - 11:00 a.m. Cortical Interactions Between Prosthetic and Natural Retinal Responses – Implications for Restoration of Central Vision
Yossi Mandel, M.D., Ph.D., Bar-Ilan University, Ramat Gan, Israel

11:00 - 11:30 a.m. **GROUP DISCUSSION**

11:30 - 12:30 p.m. **LUNCH AND POSTER AWARDS**

TUESDAY, NOVEMBER 12, 2019

Session Six: Where to from here?
MODERATOR – Edward O'Malley, M.D., Department of Ophthalmology, Henry Ford Health System, Detroit, MI

12:30 - 1:00 p.m. The Challenge to Meet the Expectations of Patients, Ophthalmologists and Public Healthcare Systems with Current Retinal Prostheses
Eberhart Zrenner, M.D., University of Tuebingen, Tuebingen, Germany

1:00 – 2:00 pm PANEL – Where to From Here? Challenges and Opportunities
Members: Joseph Rizzo, M.D. – Mini- Symposium
Harvard Medical School, Boston, Massachusetts
Robert Greenberg, M.D., Ph.D. - Lessons Learned
Alfred Mann Foundation, Valencia, California
Alfred Stett, M.D., Reutlingen, Germany
Philip Troyk, Ph.D., Illionis Institute of Technology
Eberhart Zrenner, M.D., University of Tuebingen, Germany

2:00 – 2:30 p.m. **Wrap-up – Plans for 2021!!**
Lauren Ayton, Ph.D.
David J. Goldman, M.D., M.B.A.
Philip C. Hessburg. M.D.
Roseanne Horne
Edward O'Malley, M.D.
Joseph Rizzo, M.D
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2019 World Congress:

The Eye and The Chip

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Photo from the 2017 The Eye and The Chip

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Henry Ford Health System

Applications of Deep Learning AI to Neural Signal Analysis, Sight Perception, Device Design, and Neural Stimulation Patterning

Gregory Auner, Michelle Brusatori, Changhe Huang, and Ehsan Majidi
Detroit Institute of Ophthalmology Henry Ford Hospital system, and Wayne State University

Purpose: Deep learning based artificial intelligence (AI) is a form of machine learning that enables computational systems to learn from experience and understand the world in terms of a hierarchy of concepts. Because the computer gathers knowledge from experience, there is no need for a human computer operator to formally specify all the knowledge that the computer needs. The hierarchy of concepts allows the computer to learn complicated concepts by building them out of simpler ones. The Deep Learning algorithm starts as a supervised system where a ground truth is given. For example, if we provide a signal input and tell the computer what it means the Deep Learning algorithm will begin learning how to interpret the signal even if it has variations or confounding signals mixed in. Further if we teach the Deep Learning algorithm what the signal means it will 'learn the language' of the signal. Our research involves an expansion of the use of Deep Learning based artificial intelligence algorithms to aid in the interpretation of neural signals. The Deep learning architecture is based on the neural networking of a primitive retina. The resulting neural signal analysis by the algorithm is used to optimize implantable device design as well as providing complex stimulation signals based on the 'learned' neural signal pattern required for a perceived image. The architecture of this Deep Learning algorithm and how it can be used for neural signal interpretation, stimulation patterning, and device design guidance will be presented.

Method: A real-time pre-processing unit based on convolution and deconvolution networks combined with a rearrangement unit based on prior knowledge of neural signals, and a real-time identification unit based on convolution neural networks (CNN) followed by partially connected neural network (PCNN) are used to identify the neural signals and learn how to interpret them. In turn that interpretation of the signals provides insight into how complex neural signals add perception of sight. This guides the array of simulation points and complexity of the stimulating signal required. The Deep Learning neural network was optimized and expanded to provide ever increasing accuracy. We have generated a 28 neural network based artificial intelligence nodes and provided 10000 sample signals to train the Deep Learning algorithm.

Results: Preliminary results demonstrated the capability of the Deep Learning algorithm to be taught to accurately interpreted signals even with significant variability and confounding background interference. The output from the Deep learning provided an optimized set of stimulation patterns to mimic complex signals that may be used for the perception of sight. The results also provided information on the number of isolated electrodes that may be required for providing an optimal stimulation pattern and signal form.

Conclusion: Deep learn has great potential as a tool for understanding neural signals and providing optimal stimulation signals for the perception of sight.

Biography: Dr. Gregory W. Auner is a Strauss/TEAMS (Technology and Engineering Applications in Medicine and Surgery) Endowed Chair and Professor in the Department of Surgery and Biomedical Engineering. He also has appointments in the Department of Electrical and Computer Engineering the Department of Physics at Wayne State University in Detroit, MI. He is the Director of Research for the Detroit Institute of Ophthalmology at Henry Ford Health System Department of Ophthalmology. He is the founder and director of the Smart Sensors and Integrated Microsystems (SSIM) program at WSU which encompasses 8 centrally located laboratories over 150 participating faculty, graduate students, staff scientists/engineers, and undergraduate researchers. He has developed an array of instruments, sensors and microsystems, software and communication systems for federal institutions and industry. Approximately 90% of his research involves the research and development of microsystems, nanosystems, intelligent deep learning systems and BioMEMS systems. He has performed extensive research for the Department of Defense, The National Institute of Health, the National Science Foundations, the Defense Threat Reduction Agency, and the Biomedical Advance Research and Development Authority in the areas of water borne chemical and bacteria sensing, , Radiation dosimetry in human exposure, airborne pathogen detection, signal analysis, and encrypted communications. He has been the Principal Investigator on more than $40 Million in peer reviewed funding at Wayne State University. He has over 40 patents (issued and pending) in the last several years for bio implants, chemical, biomedical, and environmental sensing with Raman spectroscopy, and microsystems lab on a chip development. He has over 300 peer reviewed publications and over 4000 citations. He has received a number of awards including Crain's Healthcare Hero Award 2018, the Strauss Endowed Chair, Induction to the 2007-2008 Class of Leaders & Innovators, WSU Alumni Faculty Service Award, RARE Foundation's Everyday Hero Award, the Award for Outstanding Contribution to the Advancement of Knowledge- American Society for Reproductive Medicine to name a few. Dr. Auner was appointed to the National Academies Board on Manufacturing Design and Engineering in 2004. He is also the Co-Founder and Chief Science & Technical Officer at Seraph Biosciences, Visca, LLC, and Venica Fluidic Sciences- Wayne State University SSIM program spin-off companies.

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Novel Vision Processing Method Facilitates Color-Contrast Object Detection in Participants Implanted with a Suprachoroidal Retinal Prosthesis

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Purpose: We evaluated a novel vision processing method [Single Image Contrast (SIC)] with recipients of the Bionic Vision Technologies suprachoroidal retinal prosthesis (NCT03406416) with end stage retinitis pigmentosa (RP). SIC aims to enhance scene understanding in scenes in which there is color contrast but similar grayscale intensity level. We aimed to determine whether SIC vision processing (VP) was more effective for the detection of tabletop objects than Lanzcos2 (Intensity) state-of-the-art VP and device off.

Method: A randomized controlled trial investigated the effectiveness of SIC VP to locate and detect objects with three participants (P2 – P4) with advanced RP (2 male, 1 female; aged 47 – 66 years) who were implanted unilaterally with the retinal prosthesis. The participants attempted to detect and touch common tabletop objects (1 of 5 randomized objects for each trial: cup, bowl, plate, placemat, soda can, in 1 of 9 grid positions). The objects were red-colored and had similar luminance, saturation and similar grayscale intensity levels to the green tabletop. The effectiveness of SIC VP was compared to current state-of-the-art Intensity (grayscale only, Lanczos2) VP and device off with order of VP presentation randomized. The outcome measures included: locate object with verbal response; and, final proximity of finger to the object.

Results: For object localization (verbal response), SIC VP was associated with significantly greater accuracy than Intensity for P2 ($p < .01$) and P3 [($p < .001$); not significant for P4], as well as significantly better performance than device off for all participants ($p < .01$). SIC VP was associated with a significantly closer final proximity of their finger to the object compared to Intensity VP for P2 ($p < .01$), P3 ($p < .01$) and P4 ($p < .01$), as well as system off ($p < .001$) for all three participants.

Conclusion: For three individuals implanted with a suprachoroidal retinal prosthesis, Single Image Contrast VP significantly enhanced the performance in comparison to state-of-the-art Intensity VP and device off in a tabletop task in color but with low grayscale intensity levels. The findings indicated that novel VP algorithms may improve functional vision in environments where objects have a similar color intensity and saturation to their surroundings. Further studies will determine whether SIC can assist with other tasks of everyday functioning such as orientation and mobility for retinal implant recipients.

Biography: Nick Barnes is an Associate Professor in the Research School of Electrical, Energy and Materials Engineering at the Australian National University. He started at ANU in 2016. He received his Ph.D. in 1999 from the University of Melbourne. He was visiting research fellow at the University of Genoa, Italy in 1999. From 2000 to 2003, he was a lecturer with the Dept Computer Science and Software Engineering, the University of Melbourne. From 2003-2019 he was at NICTA which merged with CSIRO in 2016. He became program leader of Computer Vision in 2006, where he led a research team in Computer Vision of up to 25 research staff. His research interests lie in computer vision particularly: dense prediction, 3D vision, visual saliency and visual navigation including prosthetic vision. He has published more than 140 research papers on these topics. He was one of the team of CIs of the successful bid for the ARC Special Research Initiative in Bionic Vision: 2010 to 2015. His pioneering work in vision processing for prosthetic vision was a key contribution to the formation of a spin-out company, Bionic Vision Technologies, and capital raised in 2017. This work was recognized in the CSIRO Digital and National Facilitates Science Excellence Award in 2017.

Avi Caspi, Ph.D.

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Real-time Beam Trajectory Control for Fully Wireless Optically Powered Epiretinal Prostheses

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Existing artificial vision systems rely on permanent, wired power/data connections through the sclera to an inductively coupled coil on the outside of the eye, increasing the risk to patients as well as surgical complexity and cost. A completely wireless solution provides increased safety and reduces surgery time due to the complete encapsulation of the implant inside the eye. We present a completely wireless power and data transfer system for delivering artificial vision via a fully diamond-encapsulated epiretinal prosthesis placed on the macula. All-diamond electrodes are realized with a localized ultra-nanocrystalline diamond process to provide electrical stimulation to the retina, shown in Figure 1a.

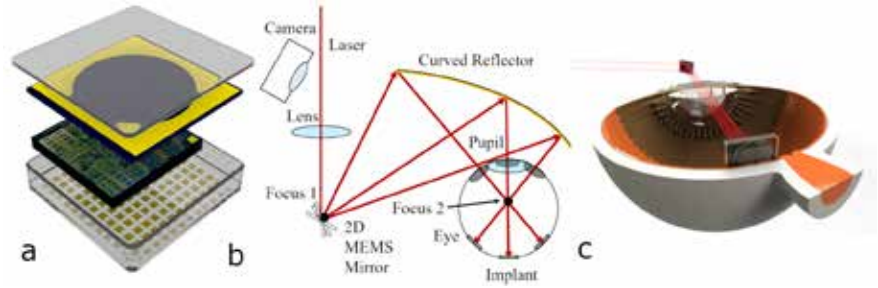

Figure 1. (a) Exploded view schematic of the implant enclosure. (b) Range of optical paths enabled by an ellipsoidal reflector geometry. (c) Schematic of the implant placed on the macula where the optical beam enters through the pupil.

A custom ellipsoidal reflector is fabricated and used to reflect an optical beam from an 850 nm laser through the pupil and onto a high-efficiency photovoltaic chip embedded inside the epiretinal prosthesis, as shown in Figures 1b and 1c. A 1:1 scale 3D-printed robotic eye system is used to characterize the optical system and dynamic performance of the beam redirection with a realistic moving pupil. Pupil coordinates are extracted at up to 90 frames per second using a pupil camera and transmitted to a microelectromechanical systems (MEMS) mirror to provide real-time direction of the optical beam in response to voluntary eye movement and pupil saccades and pupil saccades. A Kalman filter is implemented in real-time, improving the reliability and response of the beam targeting process. Additional beam trajectory corrections are developed to account for possible reflector misalignment, increasing the safety and reliability of the optical delivery system. Beam targeting is verified using a quadrant photodiode at the back of the artificial eye. A second camera is used to capture scene information which is processed to map the appropriate field of view to the effective field of view provided by the epiretinal prosthesis. We show that optical power delivery is viable strategy for future retinal implant designs.

Disclosure: This research is conducted in collaboration with iBionics Inc.

Biography: Dr. Ross Cheriton is a Postdoctoral Fellow at the National Research Council of Canada. He received his Ph.D. in Physics at the University of Ottawa's SUNLAB with research on the theory and characterization of gallium nitride nanowire intermediate band solar cells. He has authored and co-authored over 13 articles and conference proceedings. He has worked in a retinal implant startup iBionics Inc. to develop wireless retinal implants for restoring sight to the blind, where his work is featured in the Globe and Mail, the Ottawa Citizen and Le Droit newspapers. His research topics include integrated photonics, astrophotonics, III-V on silicon solar cells, multijunction solar cells, nanowire solar cells, optical phototransducer devices, high magnetic field quantum dot theory, nanostructured entangled photon sources, optical systems for wireless epiretinal implants and real-time dynamic optical power delivery. He has taught numerous seminars for university students and staff on 3D modeling using Blender for effective, high quality science visualization. His work is currently focused on novel astrophotonics devices using integrated photonic devices for exoplanet and planetary spectroscopy.

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Real Time Imaging of the Microglia Response to Electrical Overstimulation of the Retina Under Epiretinal Stimulus Electrodes.

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Purpose: We examined the microglial response to overstimulation of the retinal tissue under an epiretinal stimulus electrode in real time. Using an optically transparent stimulus electrode and confocal microscopic optical sectioning, we determined how the microglia respond spatially to injury of the retinal tissue.

Methods: We imaged the retinas of transgenic mice in which the microglia expressed a water soluble green fluorescent protein (GFP). Retinae were isolated and placed on black filter paper and superfused with oxygenated Ames media at 35°C. A thinly insulated optically transparent FEP tube 220µm diameter i.d., 295µm o.d. was placed against the retinal surface at a 30 degree angle using a micromanipulator. The retina was overstimulated for 5 minutes using 749µC/cm2/ph biphasic current pulses, 1msec/phase at 50Hz using an AC-coupled stimulus isolator. During the stimulation experiment, the retinal microglia were optically sectioned at 2.5min intervals, 20X magnification, using a Leica SP2 confocal microscope. The microglia were followed for 1 hour, and then a fluorescent DNA label for cellular damage was applied to the retina. The microglia response to overstimulation was studied at 2.5, 25, and 52.5 minutes post stimulation and analyzed at 3 concentric zones under the electrode lumen. Percent survival and morphometric parameters were studied.

Results: We found that microglial injury from overstimulation occurred very rapidly under the stimulus electrode even 2.5 minutes post stimulation, resulting in process retraction. The strongest damage occurred in a ring-like zone under the edge of the electrode where their GFP fluorescence was often lost, followed by less damage in a central zone under the electrode lumen. Microglia outside the electrode edge responded to retinal overstimulation by process in-growth under the electrode. The microglia in the periphery were largely unaffected.

Conclusions: We found the microglial injury response from electrical overstimulation is very rapid. In some cases, there is a complete loss of microglial GFP fluorescence. The retinal microglia were most damaged at the edge of the stimulus electrode. Careful effacement of the thinly insulated tube to the retinal surface was critical for evoking stimulation damage.

Biography: Dr. Cohen received his Ph.D. in the lab of Dr. Peter Sterling at the University of Pennsylvania in 1987. After postdoctoral training at the University of Minnesota with Dr. Robert Miller, and at the Jules Stein Eye Institute at UCLA with Gordon Fain, he joined the faculty in the Dept. of Ophthalmology at Yale University Medical School as a retinal physiologist in 1992. In 2000, he became a visiting professor in the Dept. of Molecular and Cellular Biology at Harvard University. Since 2003, he is a research scientist at the CDRH Office of Science and Engineering Labs at FDA.

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In-Vitro Study and Capacitive Behavior of Photovoltaic, Subretinal Implant with 3D Carbon Electrodes

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Background: Two of the most prominent retinal diseases are age-related macular degeneration (AMD) diagnosed in 700.000 persons annually in the US, and retinitis pigmentosa (RP) diagnosed in one out of 4000 live births [1]. The detailed pathophysiology of AMD and RP is unknown, but the degeneration of retinal photoreceptors is a central event leading to visual loss in these diseases. There are no effective treatments of photoreceptor degeneration. A potential solution for partial restoration of sight is to implant a photovoltaic device (solar cell), which is able to translate incoming light into electrical signals that are transmitted to the secondary neurons in the retina [2-6]. By placing numerous electrically separated photodiodes at the location of lost photoreceptors and in contact with the overlying retina, stimulation of the secondary neurons will occur when light is incident on the eye.

Palanker et al. [7, 8] has previously reported on the fabrication of a photovoltaic device with pixel sizes down to 70×70 μm2 and a responsivity of 0.36 A/W. Recently the same group reported pixel sizes of 55 μm with an observed positive impact on visual acuity in rats [9].

Purpose: Electrically active 3D interfaces between neuron and electrodes could improve contact between stimulating electrodes in subretinal photovoltaic implants and the surrounding tissue. We have previously reported on fabrication, electrical properties and biocompatibility of 3D pyrolytic carbon pillars [10], but here we report on complete photovoltaic devices for subretinal neural stimulation and prosthesis.

We propose a single diode, subretinal implant design using 3D electrodes made from pyrolytic carbon. 3D carbon electrodes may be fabricated by pyrolysis of the negative photoresist SU-8, which is very suitable for fabricating high aspect ratio microstructures with dimensions suitable for subretinal neural stimulation. Pyrolyzed SU-8 has been reported as biocompatible and able to promote adhesion of certain cells [11] to neural tissue. Thus, 3D pyrolytic carbon electrodes made from SU-8 seem promising for the application in subretinal prosthesis.

Methods: Highly n-doped regions were defined in a p-type double-side polished Czochralski (CZ) silicon wafer (4" diameter, 350 μm, 0.4 Ω-cm) using phosphorus diffusion at 900μfor 30 min with POCl3 in a Tempress tube furnace with 500 nm thermal SiO2 as mask. Carbon electrodes were fabricated with a method similar to that shown earlier [12]. SU-8(2075) was spun to a thickness of 78 μm using a Süss MicroTec-RCD8T spin coater. The polymer was softbaked on a hot plate at 50μfor 5 hours, exposed to a dose of 210 mJ/cm2 UV radiation and post exposure baked at 50μfor 5 hours. The structures were developed in PGMEA for 2x10 min, treated with a 500 mJ/cm2 UV 'flood-exposure' and a second hard bake at 90μfor 15 hours. SU-8 structures were pyrolyzed in an ATV-PE0604 furnace at 900μfor 1 hour, resulting in carbon micropillars with a height of ~35 μm. The return electrode on the rear of the device was realized by evaporated aluminum, using a Wordentec QCL800 metal evaporator.

For the determination of the capacitive behavior and charge injection properties, electrode chips with 4 mm2 working electrodes (WE) with pyrolytic carbon pillars were used. The design and fabrication of these test structures is reported elsewhere [13, 14]. The charge storage capacity (CSC) was characterized using cyclic voltammetry (CV) with 10 mM potassium hexa-cyano ferrate (II+III) in phosphate buffered saline (pH = 7) as the electrolyte. CV and transient voltammograms were measured using a CHI 1030 potentiostat and NOVA software for data collection. The scan rate was 100 mV/s in all experiments.

The maximum injectable charge Qmax for pillars and planar pyrolytic carbon electrodes, respectively, was calculated from the extracted threshold-time tth and the constant current I, i.e. Qmax=Itth/Ae where Ae is the electrode area, was determined using transient voltage measurements.

The elemental composition of the sample was characterized using X-ray photoelectron spectroscopy (XPS). The measurement and analysis was done using a Thermo Scientific K-alpha XPS tool with a monochromatic aluminum K-μsource. Avantage was used for the spectrum analysis and binding energies between 0 and 1350 eV were surveyed.

The transmission of light impulses to the inner retina was tested on freshly enucleated porcine eyes that are collected daily from Danish Crown's slaughter house in Horsens and transported to the laboratory for experimental ophthalmology at Aarhus University Hospital. The retina is removed from the choroid by hydro-dissection, followed by removal of photoreceptors. The retinal preparation is positioned on the photovoltaic array in a tissue chamber and during stimulation of the array with white light the potentials generated in ganglion cells overlying the array are recorded by intracellular electrodes. The photovoltaic chip and the dissected piece of tissue is placed in a petri dish with physiological salt solution (1.6).

Conclusion: Porcine retinal tissue potential response to light measured in vitro with photovoltaic chip; no response measured without chip. When the photovoltaic chip is present and the tissue-chip stack is illuminated with white light, an increase in membrane potential of μ0 mV is seen. Such potential increase is comparable with the potential increase measured during addition of 40 mM KCl in the same measurement setup. This indicates that the observed potential increase could be associated with neural stimulation. Future work includes measurements with a different light source, probably pulsed, near infrared (870 nm) radiation, aiming at wavelengths that do not affect the tissue, but are effectively absorbed by the Si chip.

The charge storage capacity of pyrolytic carbon was determined to 10.9 mC/cm2 for the best 3D pillar geometries and 6.4 mC/cm2 for planar carbon electrodes. Such values are comparable with those of IrOx electrodes [18, 19], which are considered the state-of-the-art and material of choice for retinal stimulation. The maximum injectable charge of similar carbon electrodes determined from transient voltage measurements was in the range 1-1.7 mC/cm2 for planar and pillar carbon electrodes. These values are encouraging for future application of pyrolytic carbon electrodes in sub-retinal implants, since retinal stimulation is possible for much lower charge densities [18, 20], while significantly higher charge densities are probably not relevant due to tissue damage thresholds [20, 21]. In future work, we expect to significantly improve the electrical properties of the pyrolytic carbon electrodes. The elemental composition of the fabricated pyrolytic carbon pillars was analyzed by XPS. The analysis showed that the pyrolysis was successful and clean, resulting in carbon electrodes that are potentially biocompatible.

Biography: Rasmus Schmidt Davidsen is a postdoc at the Technical University of Denmark (DTU), Department of Micro- and Nanotechnology, working with photovoltaic retinal implants. Rasmus Schmidt Davidsen holds a PhD 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. Furthermore, Rasmus co-founded the start-up company Black Silicon Solar, focused on commercializing the black silicon technology. 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 33 years old, lives in Copenhagen and furthermore holds a MSc, BSc 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.

Patrick Degenaar, Ph.D.
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Headset Development for Optogenetic Retinal Prosthesis

Dr Ahmed Soltan, Mr Yu Liu, Dr Patrick Degenaar, Neuroprosthetics lab, Newcastle University. Additional contributions from the Institute of Neuroscience, Newcastle University, Imperial College, Tyndall Institute, Ireland, via the previous OptoNeuro (European) FP7 project.

Abstract: Optogenetic approaches to retinal prosthesis could provide for a significant visual return if its own unique challenges are addressed. The key advantage would be genetic targeting of the ON and OFF pathways and thus perhaps a higher contrast visual return. In 2015, the first clinical trials were approved for optogenetic intervention in retinae of patients blinded by Retinitis Pigmentosa. Two companies (Retrosense – now Allergan) and Gensight Biologics are both embarking on such early testing to determine efficacy. The two primary approaches; bipolar cell sensitization, and retinal ganglion cell sensitization are respectively akin to sub-retinal and epi-retinal prosthetics. But in both cases, there will be a need for a headset which can either intensify light or intensify and perform retinal processing.

We have therefore developed a headset as per fig 1 below which provides image acquisition and processing and acts as a super-radiant display required for optogenetic approaches. The core technology is a gallium nitride micro-LED array driven by custom microelectronics which acts as a pixelated illuminator. We use modified virtual reality optics to deliver the light and have demonstrated that we can deliver sufficient irradiance in the retina. To demonstrate efficacy, we utilized a human eye model and optogenetically sensitized rodent retinae to demonstrate effective stimulation. We have also combined these studies with explorations into the regulatory framework for photochemical damage thresholds in the retina.

In the long-term, although we hope to present uptake of this approach upon successful outcomes of the ongoing trials described above, it should be further noted that although currently, microLED arrays are custom technology, they are increasingly being explored for commercial use in consumer virtual/augmented reality displays, which will allow rapid update of this technology. At the conference, we will fully describe our system, its biological testing, and long-term perspectives of the optogenetic approach to retinal prosthesis.

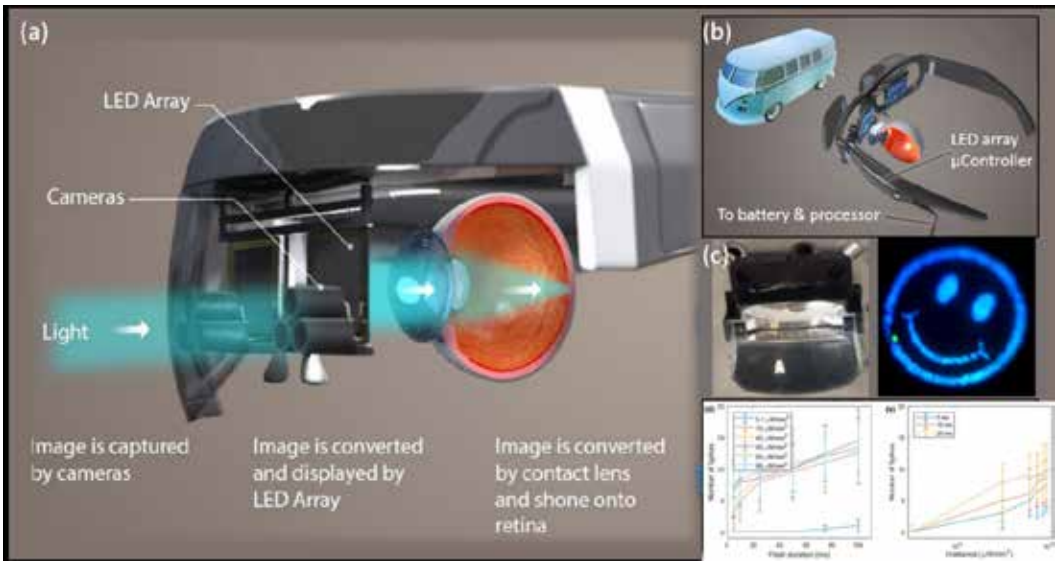

Fig. 1 (a) conceptual diagram show the proposed headset with the main components of the headset including the camera, optics and the micro-display, (b) side image of the device shows the location of the microcontroller and the battery for the device, (c) an image of the folded prism lens used in the device with an image captured after the optics on the surface of the retina to show the quality of the projected image, and (d,e) summary of the biological results from a retina after applying light pulses of different lengths.

Optogenetic gene therapy combined with an optoelectronic headset could provide for a significant visual return if its own unique challenges are addressed. In 2015, the first clinical trials were approved for optogenetic intervention in retinae of patients blinded by Retinitis Pigmentosa. Two companies (Retrosense – now Allergan) and Gensight Biologics are both embarking on such early testing to determine efficacy. The two primary approaches; bipolar cell sensitization, and retinal ganglion cell sensitization are respectively akin to sub-retinal and epi-retinal prosthetics. But in both cases there will be a need for a headset which can either intensify light or intensify and perform retinal processing.

We have therefore developed a headset which can be seen conceptually in Figure 1 below. The core technology is a gallium nitride micro-LED array driven by custom microelectronics which acts as a pixelated illuminator. We use modified virtual reality optics to deliver the light, and have demonstrated that we can deliver sufficient irradiance to drive optogenetically encoded retinae using an optic model of the eye and in-vitro optogenetic retinae. In addition, we have an embedded image acquisition and software system to acquire and process the visual information prior to delivery in the retina.

We will fully describe our system, its biological testing, and long-term perspectives of the optogenetic approach to retinal prosthesis. In particular there are specific options depending on which forms of optogenetic retinal photosensitization is most successful, and how specular the returned vision is. I.e. how uniform the genetic expression is, and the effects of retinal remodeling with retinitis pigmentosa.

Biography: Patrick Degenaar is an interdisciplinary academic in Newcastle University specialising in Neuroprosthetics. He initially received a first class (Hons.) degree in applied physics in Liverpool University, the UK in 1995 with a Winn Evans prize for the best undergraduate project. He then went on to do an M.Res in surface science before spending a short period in the medical industry working on portable ECG monitors. In 1997, he won a Monbusho scholarship to do a PhD in the Japan Advanced Institute of Science and Technology, researching bioelectronics and bio imaging at the Tamiya lab. In 2001 he graduated and spent time in the software industry in the Netherlands before returning to academia in 2002 as a post-doc in Imperial College, London, working on organic solar cells. In 2003, he shifted topic again, with a new post-doc exploring reverse engineering the human eye in microelectronics. Then in 2005, He attained an RCUK fellowship and lectureship in Imperial College to explore the new field of optogenetic neuroprosthetics. He continues this work in Newcastle after moving his team there in 2010.

Dr Degenaar's core interests lie in the development of visual prosthetics. From 2010-2014 he led a European project on optogenetic retinal prosthetics. Thereafter, he has shifted his team's focus towards visual cortical prosthetics. He is also currently the engineering team leader on a large interdisciplinary project called CANDO which aims to develop a clinical grade optogenetic system for epilepsy (trials aimed for mid-2020's), which would act as a first stage towards visual prosthesis.

Jessy Dorn, Ph.D.
Second Sight Medical Products
Sylmar, California

Orion Visual Cortical Prosthesis System: One-Year Clinical Trial Results

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2. University of California, Los Angeles, Department of Neurosurgery 3. Baylor College of Medicine, Department of Neurosurgery

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

Methods: This is a five-year, prospective, non-randomized, single-arm early feasibility study (clinicaltrials.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. There are six subjects between two study centers.

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. Adverse events are collected throughout the study; performance is assessed at 6 months, 12 months, and 24 months with the Functional Low-vision Observer Rated Assessment (FLORA), visual function tests, and patient-reported outcomes.

Results: Six subjects have been implanted at UCLA and Baylor College of Medicine, five males and one female. As of May 31, 2019, average implant duration was 12.1 months (range 4.4 – 16.0). Average age at time of implant was 48.6 years. Cause of blindness included trauma, endophthalmitis, and pediatric glaucoma. All subjects had bare or no light perception at the time of implant, but were previously sighted.

The Orion was implanted successfully in all 6 subjects. One serious adverse event due to the device (seizure) has been reported; 5 non-serious adverse events due to the procedure or device were reported. All subjects perceive light from stimulation. All subjects completed the custom-programming and spatial mapping process and were cleared to use their Systems outside the hospital. At that point, all began a program of visual rehabilitation. At six months post-implant, 2 of 5 subjects were rated as having received "positive" benefit from the Orion System in their everyday life, and 3 of 5 were rated as having received "mild positive" benefit. None were rated as neutral or negative. On Square Localization, 3 of 5 subjects performed significantly better with their System ON than OFF; on Direction of Motion, 2 of 5 performed significantly better ON than OFF; none of the subjects were able to score on Grating Visual Acuity with the System ON or OFF. Full 12-month results for the first five subjects will be reported once data collection is complete. Results will be compared to those gathered in pre- and post-market studies of the Argus II Retinal Prosthesis System, a commercially-approved device to create artificial vision in users blind from retinitis pigmentosa.

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.

Biography: Jessy Dorn has worked at Second Sight Medical Products, a medical device company that developed the Argus II and Orion I visual prosthesis systems, since 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, principles of neurostimulation, low vision outcome measures, and human visual psychophysics. She received her Ph.D. in Neuroscience from UCLA, studying primate visual cortex, and her BA in Biology from the University of Chicago.

Cordelia Erikson-Davis, PH.D.
Stanford University
Stanford, California

Helma Korzybska, Ph.D.
Paris Nanterre University
Paris, France

The Perceptual Experience of Artificial Vision: Qualitative Reports of Epiretinal Implant Users

Introduction: Retinal implants have now been approved and commercially available for certain clinical populations for over 5 years, with hundreds of individuals implanted, scores of them closely followed in research trials. Despite these numbers, however, few data are available that would help us answer basic questions regarding the nature and outcomes of artificial vision: what do participants see when the device is turned on for the first time; how does that change over time?

Methods: Semi-structured interviews and observations were undertaken as part of ethnographic study of epiretinal prosthesis recipients at the Quinze-Vingts and Moorfields Eye Hospitals from 2016 to 2018. This resulted in interview and observational data on 15 participants who received the Argus I, Argus II, IRIS I or IRIS II devices, collected at the hospital at various points in the process that participants go through in receiving the device, including evaluation, implantation, initial activation and systems fitting, reeducation and life after. These data were supplemented with interview data with vision rehabilitation specialists at the clinical sites as well as clinical researchers at Second Sight and Pixium. Observational and interview data were transcribed, coded and analyzed using an approach guided by Interpretative Phenomenological Analysis (IPA). Data were then compared across field sites to identify common themes.

Results: The perceptual experience produced by these devices is described by participants as fundamentally, qualitatively different than natural vision. It is a phenomenon they describe using terms that invoke electric stimuli, and one that is ambiguous and variable across and sometimes within participants. Artificial vision for these subjects is a highly specific learned skillset that combines particular bodily techniques, associative learning and deductive reasoning to build a "lexicon of flashes" - a distinct perceptual vocabulary - that they then use to decompose, recompose and interpret their surroundings. The percept does not transform over time; rather, the participant can better learn to interpret the signals they receive. This process never ceases to be cognitively fatiguing, and does not come without risk nor cost to the participant. In exchange participants can receive hope and purpose through participation, as well as a new kind of sensory signal that may not afford practical or functional use in daily life, but for some provides a kind of "contemplative perception" that participants tailor to individualized activities.

Conclusion: Attending to the qualitative reports of participants regarding the experience of artificial vision provides valuable information not captured by normative functional outcome measures. These data can both inform device design and rehabilitative techniques, as well as grant a more holistic understanding of the phenomenon of artificial vision.

Biography : Cordelia Erikson-Davis is a M.D./Ph.D. candidate at Stanford University, School of Medicine. Her research focuses on perceptual experiences associated with brain-machine interface devices (focusing on visual prostheses), and the institutional processes (i.e., academic, commercial and regulatory) by which these devices move from bench to bedside in the U.S. and Europe.

Helma Korzybska is a Ph.D. candidate in Cultural and Social Anthropology at Paris Nanterre University, at the Laboratory of Ethnology and Comparative Sociology (LESC). Her research focuses on the experiences of individuals having lost their vision or hearing, and the challenges and impact of the substitution of sensory organs by equipment systems (retina and cochlear implants). H. Korzybska's approach centers on how people who have lost the function of an organ adopt prostheses and thus reconfigure their relationship to the environment. This research includes close observation of the sensory-motor re-education guided by both a medical team and electrical engineers, and analysis of their roles in the formation of a specific "perceptive mode", determining a certain "mode of existence". By studying this particular medium towards human "reparation", she interrogates the possible coexistence of the natural with the artificial, of the biological with the technological.

Long-Sheng Fan, Ph.D.
Iridium Medical technology &
National Taiwan University
Taiwan, Republic of China

The High Resolution Imaging Retinal Prosthesis (HARP4k) -- Status Update on Tissue Tolerance

L.-S. Fan1, S, Y. Lin1, C.L. Chang1, E. Yang1, J. Hsu1, KW Chang1, Z. -T. Lai2, T. C. Chen2, C. H. Yang2, 3, C. G. Cheng1, 4, 1. Iridium Medical Technology Corporation, 2. Dept. of Ophthalmology, National Taiwan University Hospital, 3. School of Medicine, National Taiwan University, 4. Shin Kong Hospital

Purpose: To study the retinal tissue tolerance of large implanted subretinal devices, IMTC's HARP4k Retinal Prosthesis System is used. The core of HARP4k implant is a passivated 5 mm round CMOS Imaging chip 30um in total thickness with 4,000 working electrodes integrated, 40 um in pitch. The sheer size of the implanted device in the sub-retina space could influence both inner and outer retinal blood profusion and also impose mechanical stresses to retinal tissue.

Method: To study the mechanical interactions between an eyeball and the subretinal implant, we developed a 3D computer model including the linear and nonlinear characteristics of retina tissue and implant, the retina to choroid adhesion/detachments energy, the retinal prosthesis interface contacts to choroid and retina. To evaluate the influence of the large subretinal device on retinal tissue in vivo, we use Lang-Yu minipigs as the animal model. Follow-up's of post-implant swine retina conditions are carried out and imaging data from OCT (Optical Coherence Tomography), FA (Fluorescein Angiography), and ICGA (Indocyanine Green Angiography) are collected and analyzed. Retinal OCT images are acquired at fixed interval: 2, 4, 8, 12, 16 weeks post-implant. FA and ICGA images for implant area are acquired 4 weeks after implant surgery.

Result: The computer simulation result of the mechanical stresses exerted on retinal tissue (using the 3D finite element method) is within the retinal elastic limit and the tearing energy is beneath the retina/RPE adhesion energy. The OCT images show that the retina maintains expected thickness without cyst and is well attached to the chip, and the FA/ICGA angiographies show no sign of vessel leakage during the post-implant interval observed.

Discussion: In subretinal implant device development; the retinal tolerance is a main consideration determining how large a device chip can be implanted. The study indicates that the IMTC HARP4k implant size is within the retinal tolerance.

Biography: Long-Sheng Fan received his M.S. & Ph.D. degrees in Electrical Engineering and Computer Sciences from the University of California at Berkeley. He joined IBM Almaden Research Center as a Research Staff Member developing micro technology for information storage. He has served as a section editor for Sensors and Actuators (1994-1997), A government consultant and a member of proposal review panel of NSF and NIH, and the Technical Program Chair of IEEE Transducers 2011. Dr. Fan joined National Tsing-Hua University as a Tsing-Hua Professor and the Director of the Institute of Nano Engineering and MicroSystems during 2003-9, a visiting Professor in EECS, UC, Berkeley 2010-11 and he was the coordinator of Heterogeneous Integration Program of the SoC National Program in Taiwan, promoting MEMS IP reuse with standard process modules & EDA for MEMS/IC co-design. Dr. Fan is an IEEE Fellow, and he is currently leading Iridium Medical Technology Company developing neural prosthesis.

Eduardo Fernandez, M.D., PhD.
University Miguel Hernandez
(Spain), CIBER BBN (Spain)

Towards a Cortical Visual Neuroprosthesis for the Blind: Preliminary Results in Human (Clinical Trial: NCT02983370)

Introduction/Purpose: Cortical prostheses are a subgroup of visual neuroprostheses capable of evoking visual percepts in profoundly blind people through direct electrical stimulation of the occipital cortex. This approach may be the only treatment available for blindness caused by glaucoma, end-stage retinal degenerations, optic atrophy or trauma to the retina and/or optic nerves.

Materials and Methods: A 57-year-old female with bilateral optic neuropathy and no light perception for 16 years was implanted for 6 months with an array of 100 intracortical microelectrodes based on the Utah Electrode Array (UEA). The UEA was implanted in the right visual cortex, nearby the occipital pole (O1) using a minicraniotomy. We collected multielectrode recordings and descriptive feedback regarding thresholds, features of evoked perceptions and stimulation parameters to investigate if the volunteer could integrate the electrical stimulation of visual cortex into meaningful perceptions. All the experiments were carried out at the Hospital IMED Elche during the early post-surgical period and, afterward, in a human neurophysiology laboratory at the Miguel Hernández University (Spain).

Results: The surgical implantation was performed without complications and high-quality simultaneous recordings were consistently obtained. A training period was necessary until the subject was able to distinguish between natural (spontaneous phosphenes) and artificial visual perceptions. Microstimulation mainly evoked elementary phosphenes at stable locations in visual space, described as isolated and spatially localized spots of light. Less frequently shadows or black spots were induced. All the phosphenes were in the left visual field but the electrophysiological recordings do not always correlated well with the perceptions. In this context, we found that electrical stimulation can induce either stimulation and/or inhibition of the neurons surrounding the electrodes being stimulated. When several electrodes were stimulated simultaneously the subject reported the perception of complex patterns. No adverse effects have been reported to date.

Discussion: Our preliminary results suggest that electrical microstimulation of occipital cortex in long-term blind individuals is able to provide meaningful visual perceptions. However, there are still a relevant number of open questions and more experiments should be done to achieve the clinical goals envisioned by this new technology.

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.

Ione Fine, Ph.D.
University of Washington
Seattle, Washington

Pulse Trains to Percepts: The Challenge of Creating a Perceptually Intelligible World Based on Cortical Stimulation of Early Visual Areas.

Fine, I1, Boynton, GM1, Rokem, A2,3, Beyeler M1-3 1Department of Psychology, 2eScience Institute, 3Institute for Neuroengineering, University of Washington

Introduction: The field of cortical sight restoration prostheses is making rapid progress: clinical trial for one cortical prosthesis is underway (Second Sight Medical Products, Orion (Bosking, Beauchamp et al. 2017, Beauchamp, Bosking et al. 2018), with another expected in 2020 (Troyk 2017). Stimulating the cortex to produce interpretable percepts provides its own set of unique benefits and costs. The massive expansion of the foveal representation in V1 could allow for relatively high sampling of spatial position, as compared to retinal stimulation. However, V1 receptive field sizes are relatively large, even in the fovea - almost 1 degree of visual angle. Moreover, orientation and ocular dominance columns are relatively large: (>2mm for a full ocular dominance/pinwheel map, Obermayer and Blasdel 1993, Adams, Sincich et al. 2007), so stimulation with extremely small electrodes may create elongated percepts that are binocularly rivalrous. Here we describe a computational model based on V1 neurophysiology that predicts the perceptual experience of cortical prosthesis patients across a wide range of implant and stimulation configurations. Methods and Results Written in Matlab, the model has a modular structure designed to make it easy to simulate novel implants and stimuli. The model successfully predicts a wide range of cortical stimulation psychophysical data describing the location, size and brightness of electrically induced percepts, Figure 3.

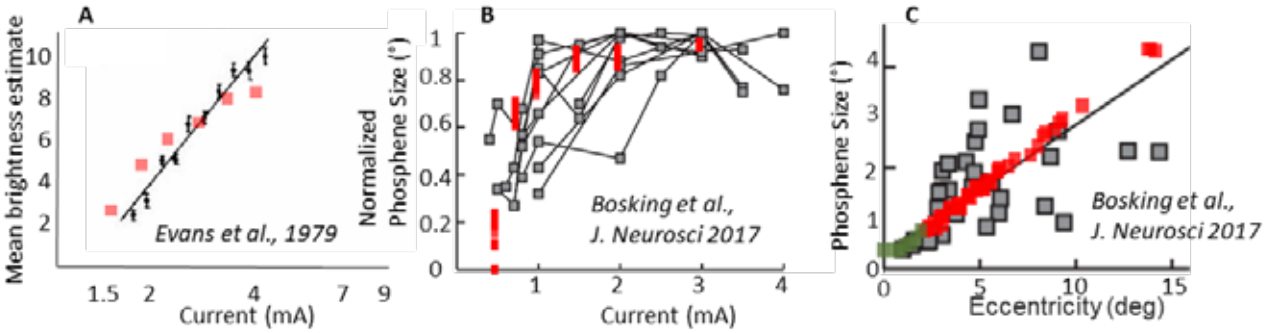

Figure 3. Our model can predict psychophysical data across a wide range of studies. Red squares show simulations of physical electrodes, grey symbols represent data. Three examples are shown. (A) Apparent brightness as a function of current (Evans, Gordon et al. 1979), (B) Normalized drawn phosphene size as a function of current (Bosking, Sun et al. 2017), and (C) Drawn phosphene size as a function of eccentricity (Bosking, Sun et al. 2017). In C green symbols show simulated electrodes near the fovea.

Our simulations suggest that, for a fixed electrode size, phosphene size generally increases linearly as a function of eccentricity, due to increases in receptive field size. At the fovea, as shown by the green symbols in Panel C, this linear slope flattens to a lower limit where phosphene sizes are ~0.77 degree diameter, regardless of electrode size. Indeed, our simulations predict no appreciable difference in phosphene sizes for electrodes ranging between 0.01-1 degree radii, regardless of eccentricity, suggesting that neurophysiological rather than engineering constraints are likely to limit the spatial resolution of cortical prostheses.

Conclusions: Models such as these provide useful tool to accelerate the development of visual prostheses and stimulation protocols.

Biography: Dr. Fine received her undergraduate degree from Oxford University, her Ph.D. from the University of Rochester and completed postdoctoral research at the University of California, San Diego. After a brief period in the Ophthalmology Department at the University of Southern California and working for Second Sight Medical Products she moved to the University of Washington, Seattle, where she is now a Full Professor. Her research examines perceptual learning and plasticity with an emphasis on the effects of visual deprivation. Current work includes measuring performance in patients who have been implanted with electrode retinal prostheses, and examining the effects of long-term visual deprivation. She is a Fellow of the Optical Society of America and the past chair of the vision section of OSA.

Shelley I. Fried, Ph.D.
Massachusetts General hospital
Boston, Massachusetts

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
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4Department of Electrical and Computer Engineering, University of California San Diego, La Jolla, CA, 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 electrodes can be avoided.

Methods: A series of computational models along with in vitro and in vivo experiments have been used to evaluate the efficacy of magnetic stimulation. 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 experiments measure cortical surface activity (ECoG) in response to electric or magnetic 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 an electrode) inserted through a hole in the center of the recording array.

Results: Simulations revealed that multiple bends at the coil tip enhanced selectivity but also reduced sensitivity. In vitro experiments confirmed these findings. Electric and magnetic stimulation both elicit ECoG responses, although electrodes activate a spatially expansive area, often more than 1 mm from the stimulation site, while activation from coils is confined to a focal area around the stimulation site (approximately 300 μm in diameter). In vitro testing of human cortical tissue (resected during medically-necessary neurosurgical procedures) revealed comparable sensitivity of individual neurons in both species.

Conclusions: Our experiments to date continue to support the viability of micro-coils as an effective alternative to conventional micro-electrodes. The focal activation from coils supports the creation of independent phosphenes that can be summated to produce more spatially-complex percepts. Future efforts include psychophysical testing in NHPs and long-term stability testing in rats.

Biography: Shelley Fried is an Associate Professor in the Department of Neurosurgery at Harvard Medical School and a Health Scientist at the Boston VA Medical Center, both in Boston, MA. Dr. Fried has a Ph.D. in Vision Science from UC Berkeley where he studied the mechanisms by which the normal retina transforms light into neural signals. He did postdoctoral training at both UC Berkeley and at the Massachusetts General Hospital in Boston studying electric stimulation of the retina. His research explores how and why neurons respond to artificial stimulation with the goal of developing improved methods and strategies. Active areas of research include electric stimulation of the retina, magnetic stimulation of primary visual cortex and the function of the early visual pathways. Prior to obtaining his Ph.D., Dr. Fried worked for 12 years in the medical device industry developing a wide range of anesthesia and respiratory therapy products.

PLATFORM SPEAKERS

Robert Greenberg, Ph.D.
Albert Mann Foundation
Valencia California

Dr. Greenberg is the Executive Chairman of The Alfred E. Mann Foundation for Scientific Research, an independent non-profit medical device incubator committed to developing and commercializing innovative solutions for significant unmet or poorly met medical conditions.

Dr. Greenberg was previously CEO and Chairman of Second Sight Medical Products (EYES), a company he led as CEO from its inception in 1998 through 2015. Under Dr. Greenberg's leadership, Second Sight, which Dr. Greenberg co-founded while working at the Alfred E. Mann Foundation, successfully developed and marketed an implantable retinal prosthesis, the Argus II, the world's most advanced implantable neural stimulator, which restores useful vision to patients blinded by Retinitis Pigmentosa, allowing them to achieve greater independence. He oversaw the FDA approval, unprecedented outpatient Medicare reimbursement of approximately $150k, with sales rising to a $10M annualized run-rate, and a successful IPO on NASDAQ, with a $550M market cap at the end of his CEO tenure. More recently, while Chairman at Second Sight, Dr. Greenberg oversaw the successful development and human implantation of a wireless cortical visual prosthesis, the Orion, which has the potential to eliminate nearly all forms of blindness.

Dr. Greenberg was also an Independent Director at Pulse Biosciences (PLSE), a company developing therapies based on nanosecond pulsed electric field technologies for oncology and dermatology applications. He was a Medical Reviewer at the Food and Drug Administration's Office of Device Evaluation. Dr. Greenberg is also currently the Chairman of the Board of Directors at the Southern California Biomedical Council, a nonprofit trade association supporting the healthcare industry in the Greater Los Angeles region.

Dr. Greenberg is the recipient of numerous honors and awards including the Edison Gold - Science/Medicine Category, the World Technology Award for Health and Medicine, the Foundation Fighting Blindness Visionary Award, and the Ophthalmology Innovation Summit Award. He has over 260 issued US patents and over 100 international patents. He received MD and PhD degrees from The Johns Hopkins School of Medicine in Baltimore, Maryland. In addition, Dr. Greenberg has published over 60 peer-reviewed publications. He has been a member of the New York Academy of Sciences, a Fellow of the American Institute for Medical and Biological Engineering, a Fellow of the National Academy of Inventors, and a Fellow of the IEEE.

Tianruo Guo, Ph.D.
University of New South Wales
Sydney, Australia

Replicating a More Physiological Retinal Neural Code Using High-Rate Electrical Stimulation

Tianruo Guo1, Madhuvanthi Muralidharan1, Mohit Shivdasani1, David Tsai1, Shelley Fried2, Liming Li4, Socrates Dokos1, John W Morley3, Nigel H Lovell1, 1. Graduate School of Biomedical Engineering, UNSW, Sydney, NSW 2052, Australia 2. Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA 3. School of Medicine, Western Sydney University, Penrith, NSW, Australia 4. School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

Rationale: One of the key reasons for the poor performance provided by current state-of-the-art neural stimulators is the inability of artificial electrical stimulation to reproduce the exquisite neural patterns that arise in different neural pathways due to indiscriminate activation of multiple parallel neural pathways. In this study, we performed in vitro patch-clamp investigations to test the possibility of controlling neuronal activity of functionally-identified retinal ganglion cells (RGCs) over a wide range of electrical stimulation parameters. RGC populations are classified into transient (ON-T and OFF-T) and sustained (ON-S and OFF-S) cells (1). Sustained cells are typically used to identify the form, shape and size of the visual input whilst transient cells are used to identify the motion or location of the visual input (2). Given that these four types serve different roles in vision perception, this work represents an important step towards replicating the retinal neural code to enable better conversations with the brain.

Methodology: Retina (N=52 from 30 mice) extracted from WT C57/BL6 mice were stimulated at amplitudes between 10-240 uA and frequencies between 1 – 6 kHz with a stimulation duration of 300ms. All neuronal responses were observed after application of synaptic blockade. Transient and sustained cell selectivity was defined as the ratio of the averaged total spike number of one RGC type over the other. Ratios higher than 1.5 were considered as preferential activation.

Results: Results indicate that epiretinal activation of ON-S, ON-T and OFF-T RGCs can be preferentially controlled in their cell-specific stimulus parameter spaces. OFF-T activation can be maximised between 1 – 4 kHz and 150 – 240 μA. ON-T between 4 – 6 kHz and 200 – 240 μA and ON-S between 3 – 6 kHz and 80 – 100 μA. OFF-S activation was not statistically significant across all frequencies and amplitudes. Furthermore, our results also indicate that a similar activation map exists for short stimulation durations of 50 ms.

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

Biology: Dr TIANRUO GUO is currently a postdoctoral research fellow at the Graduate School of Biomedical Engineering, UNSW Sydney, Australia. Guo's research has involved both (1) a basic science approach, using computational models to assess the mechanisms underlying differential excitation of functionally-distinct retinal pathways by electrical stimulation, and (2) a translational approach, developing smart stimulation strategies for neuroprostheses that elicit direct physiological neural encoding, with current applications in the treatment of retinal degenerative diseases. These studies remain highly important in both the implantable bionics and neural engineering fields related to ophthalmology as they address major challenges of being able to restore the natural processes that occur with normal vision through more accurate control of retinal neurons. Guo's role at UNSW has been the development of a novel electrical stimulation technique allowing different visual pathways to be selectively excited.

Frank Lane, Ph.D.
Illinois Institute of Technology
Chicago, Illinois

Educational Techniques to Enhance Comprehension of Complex Information

Research has concluded that information on cortical visual prostheses is complex and difficult to understand and comprehend by the individual recipient of the prosthetic device. Misunderstanding of information can include false expectations of the device, misunderstanding of the functional ability that will result from use of the device, the experimental versus therapeutic nature of the device. Misunderstanding in turn results in poor decision-making. The current project presented information about the intracortical visual prosthesis device to three groups of individuals who were blind and prospective recipients of an ICVP device. Attendees in the first group were then surveyed to assess understanding and comprehension of information. Information content and presentation techniques were then modified for groups two and three and survey outcomes were compared between the three groups' presentation formats. The results of the outcomes will be presented including implications for misunderstanding of information. Best practices for presentation of information will be presented. Implications for the informed consent process will be discussed.

Biography: Dr. Frank Lane is an Associate Professor and Chair of the Department of Psychology at Illinois Institute of Technology in Chicago, Illinois. Dr. Lane has spent the majority of his career attempting to understand the perspectives of people who are blind on assistive technology with particular emphasis on implant technology. His work has improved the overall understanding of perceived risks, functional and psychological benefits, motivation and decision-making process of cortical visual implants by implant recipients. His work has been funded by the United States Department of Education, Rehabilitation Services Administration (RSA), the United States Army, Telemedicine and Advanced Technology Research Center (TATRC), and the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Lane has used the knowledge generated by his body of research, which consists of interviews with prospective participants and individuals previously implanted, to develop education modules, recruitment and screening protocols and follow-up monitoring models for the intra-cortical vision prosthesis project at IIT.

William LeMaire, Ph.D.
Canada-Australia Bionic Vision Collaboration
Sherbrooke, Canada

A Fully Wireless 288 Electrodes Retinal Implant with an Optical Data and Power Link with Ultrananocrystaline Diamond Electrodes

William Lemaire, Marwan Besrour, Maher Benhouria, Konin Koua, Gabriel Martin-Hardy, Wei Tong, Melanie Stamp, Arman Ahnood, David Garrett, Rob Hilkes, Steven Prawer, Jim Patrick, Sébastien Roy, Réjean Fontaine

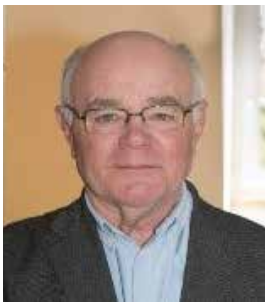
Purpose: Age-related macular degeneration and retinitis pigmentosa are two prevalent causes of blindness with limited treatment possibilities. Clinical trials demonstrated the capacity to elicit visual percepts by electrically stimulating the remaining neurons according to an image captured by an external camera. These implants transmit the data and power with an inductive link requiring percutaneous cables traversing the eye-ball. Although these implants demonstrate promising possibilities to partially restore the sight with neurostimulation, two factors currently limit the clinical outcomes: A) the restored visual acuity is bounded by the electrode density and B) percutaneous cables yield complex surgery and increase infection risks. To overcome the limitations of the cables, an implant based on a microphotodiode array converting the light from an infrared projector to stimulation pulses was recently proposed. However, the direct photodiode amplification mechanism prevents from using multipolar stimulation strategies that provide avenues to improve the visual acuity without increasing the electrode density. To alleviate limitations of current implants, we propose to A) transmit both power and data through an optical link and B) decouple this link from the stimulation by embedding a digital controller capable of multipolar stimulation strategies. A wireless implant with this approach capable of operating within the 36 mW safety limit for ocular optical power has yet to be demonstrated.

Method: To validate the feasibility of this power and data delivery method, we designed a 288 electrodes implant ASIC in CMOS 65 nm packaged in a ultrananocrystaline diamond (UNCD) enclosure. It embeds a 1 Mbits/s optical data link, 288 UNCD electrodes with a 150 µm pitch, an ADC to measure the electrode-retina impedance and a digital controller capable of multipolar stimulation. We electrically test the device by delivering power and data with an 850 nm, 35 mW laser to the integrated photovoltaic cell and photodiode. We measured the power consumption while stimulating through a 10 kΩ resistor.

Results: The measured implant static power consumption is below 2.5 mW, and 0.8 mW for an active electrode stimulating at 100 µA. This results in the possibility of activating 9 electrodes simultaneously with 10 mW of recovered power.

Conclusion: The capacity of stimulating with up to 9 electrodes simultaneously confirms the feasibility of the approach in terms of power consumption.

Biography: William LeMaire received the B.S. degree in computer engineering and the M.S. degree in electrical engineering from Université de Sherbrooke, Québec, Canada, in 2014 and 2018. He is currently a Ph.D. candidate at the Université de Sherbrooke where he focuses on the design of medical apparatus including time-of-flight positron emission tomography scanners (PET) and photovoltaïc retinal prosthesis. His current research interests include retinal implant integrated circuit design and retinal stimulation strategies.



Yannick Le Mer, M.D.
Pixium-Vision
Paris, France

Implantation of the Wireless Subretinal PRIMA Microchip in First Human Clinical Trial for Dry AMD

Yannick Le Mer 1 ,Daniel Palanker 2,3 , Ralf Hornig 4 , Guillaume Buc 4 , M. Deterre 4 , Jose A. Sahel 1,5 (1) Ophthalmology, Foundation Rothschild, Paris, France (2) Ophthalmology, Stanford University, CA (3) Hansen Experimental Physics Laboratory, Stanford University CA, (4) Pixium Vision, Paris, France (5) Ophthalmology, University of Pittsburgh, PA

Purpose: The Prima system, including a wireless subretinal photovoltaic microchip, is designed for restoration of central vision in patients blinded by retinal degeneration while preserving the residual peripheral field. Minimal invasive surgical implantation technique was designed to make subretinal implantation as safe as possible

Methods: A prospective single-center study of feasibility and safety in 5 patients with no central foveal perception and residual peripheral visual acuity ≤20/400 in the treated eye due to geographic atrophy. For each patient, the first step was to determine the location of the main PRL in the periphery by microperimetry to plan surgery accordingly. The retinotomy was made distally from this area. Surgical technique included a complete vitrectomy, detachment of the posterior pole with subretinal BSS injection, achieved completely in 4 cases with manual dissection of the atrophic macula, creation of a 2.2 mm retinotomy for the 2x2 mm microchip, insertion of the microchip under the macula with vertical forceps, injection of perfluorocarbon liquids to stabilize the macula, finally exchanged with either silicone oil or gas. No photocoagulation was done to avoid increasing the lesion of the optic fibers.

Results: In all 5 patients, the microchip was successfully implanted under the macula and remains stable, with a follow-up reaching 18 months in the first patient and 12 months in the last patient. In 3 patients the microchip was placed into an optimal position centrally and close to the fovea. In 2 patients the microchip was within the scotoma but in suboptimal positions– one in the choroid and another paracentral. The first patient operated under local anesthesia, moved the head when the vertical forceps and the chip were being maneuvered under the retina, ending up with a subretinal bleeding masking the implantation area. The chip was pushed under the retina without adequate visual control and ended up under the retinal pigment epithelium. In the fourth patient, the chip was placed under the fovea and gas was used as final tamponade. Control on postoperative day showed the microchip had shifted slightly to the inferior margin of the scotoma. Using totally opaque feasibility study glasses, all 5 patients perceive white-yellow patterns with adjustable brightness in retinotopically correct locations, within previous scotoma with no foveal perception. The 3 patients with optimal placement of the subretinal microchip recognize complex patterns, letters and sequence of letters, demonstrating visual acuity elicited from the central atrophic area with no pre-surgery foveal perception, to reach 20/460-20/550 post implantation of PRIMA in this central atrophic zone, just 10-30% below the theoretical resolution limit for this pixel size (20/420). Without the system, all patients had the same visual acuity as in their preoperative vision.

Conclusions: Wireless photovoltaic microchip PRIMA can be safely implanted under the atrophic macula and restore useful central visual perception, while preserving peripheral vision. Improvements of surgical tools such as using a specifically designed delivery system may help further to make implantation easier and avoid suboptimal positioning of the microchip. A larger multicenter European pivotal study is planned to further evaluate the PRIMA system in atrophic dry AMD.

PLATFORM SPEAKERS

Biography: Dr. Yannick Le Mer completed medical school at Paris-Descartes University, followed by a residency program in ophthalmology at the National Center of Ophthalmology (Quinze-Vingts Hospital) in Paris.

Following a fellowship in the vitreo-retinal unit (Pr Jean Haut) in Quinze-Vingts Hospital, Dr le Mer became a consultant in Germany (Phillips University in Marburg with Pr P. Kroll) and came back to France to become Head of the Ophthalmology Department in Montreuil Hospital.

In 2002 he joined Pr. JA Sahel in his vitreo-retinal department in Foundation Ophtalmologique A. de Rothschild, Paris, France where he is still a consultant after an interruption of one year as visiting professor in the Eye Hospital Jules Gonin in Lausanne, Switzerland

Dr Le Mer is member of several scientific societies and has been president of the Club Jules Gonin.

His main fields of interest are the surgical retina pathologies (retinal detachment, macular pathologies, diabetic retinopathy) and he has been involved in artificial vision since 2005 by collaborating in the IRIS projects from IMI in Germany first, and then with Pixium-Vision.

Dr. Yannick Le Mer completed medical school at Paris-Descartes University, followed by a residency program in ophthalmology at the National Center of Ophthalmology (Quinze-Vingts hospital) in Paris.

Following a fellowship in the vitreo-retinal unit (Pr Jean Haut) in Quinze-Vingts hospital, Dr le Mer became a consultant in Germany (Phillips University in Marburg with Pr P. Kroll) and came back to France to become Head of the Ophthalmology Department in Montreuil Hospital.

In 2002 he joined Pr. JA Sahel in his vitreo-retinal department in Foundation Ophtalmologique A. de Rothschild, Paris, France where he is still a consultant after an interruption of one year as visiting professor in the Eye Hospital Jules Gonin in Lausanne, Switzerland

Dr Le Mer is member of several scientific societies and has been president of the Club Jules Gonin.

His main fields of interest are the surgical retina pathologies (retinal detachment, macular pathologies, diabetic retinopathy) and he has been involved in artificial vision since 2005 by collaborating in the IRIS projects from IMI in Germany first, and then with Pixium-Vision.

Yossi Mandel, M.D., Ph.D.
Bar-Ilan University
Ramat-Gan, Israel

Cortical Interactions between Prosthetic and Natural Retinal Responses – Implications for Restoration of Central Vision

Electronic restoration of central vision in age-related macular degeneration (AMD) involves a combination of prosthetic vision in the central macula, along with natural vision in the periphery. Here we studied the cortical interactions between visible and prosthetic retinal responses and compared them to interactions between the corresponding natural stimuli.

Subretinal implantation of the 1mm-diameter photovoltaic arrays in wild-type rats induced a localized degeneration of the photoreceptors above the implant, whereas the surrounding retina was left intact, similar to localized retinal degeneration in AMD. Using a customized projection system, we induced prosthetic and natural retinal stimuli with NIR (910nm) and visible light (532nm), respectively. Each presentation consisted of a central 1mm prosthetic or visible stimulus encircled by a 3mm visible surround. We recorded visually evoked potentials (VEP) in response to either non-patterned (flash or contrast step) stimuli or to complex grating patterns.

Responses to both visible and prosthetic flash stimuli decreased with increasing brightness of the continuous visible light background. Combined prosthetic and natural non-patterned stimuli (flashes and contrast steps) exhibited a linear cortical summation. In contrast, responses to alternating gratings composed of either a visible or prosthetic central area surrounded by visible grating flankers revealed significant lateral inhibition. For both prosthetic and visible targets, lateral inhibition increased with the target contrast, reaching a maximum inhibitory effect of 40%. For both natural and combined natural and prosthetic stimuli, the inhibition was eliminated by a GABAa-inhibitor, suggesting that the mechanism underlying the lateral inhibition is mediated by GABA.

The striking similarities between cortical responses to natural patterns and to combined prosthetic-natural stimuli indicate that the basic processing interactions in the visual cortex are preserved. These results support the assumption that prosthetic central vision may co-exist with natural peripheral vision in AMD patients.

Biography: Dr. Mandel is an Associate Professor in the School of Optometry and Visual Science and Institute for Nanotechnology and Advanced Materials (BINA), Bar-Ilan University, Israel. He is a medical doctor and ophthalmic surgeon and holds a Ph.D. in bioengineering from the Hebrew University, Jerusalem. His research is focused on various ophthalmic technologies aimed at restoration of sight, such as retinal prosthesis, stem cell and combination of these modalities. Of other interest are the development and study of novel nanoparticles for ocular drug delivery for treatment of AMD.

Daniel Palanker, Ph.D.
Stanford University
Stanford, California

Photovoltaic Restoration of Sight in Age-Related Macular Degeneration

Daniel Palanker1,2, Yannick Le Mer3, Thomas Flores2, Elton Ho2, Tiffany Huang2, Theodore Kamins2, Ralf Hornig4, Guillaume Buc4, M. Deterre4, Khalid Ishaque4, Jose A. Sahel3,5, K. Mathieson6(1) Ophthalmology, Stanford University, CA (2) Hansen Experimental Physics Laboratory, Stanford University, CA (3) Ophthalmology, Foundation Rothschild, Paris, France (4) Pixium Vision, Paris, France (5) Ophthalmology, University of Pittsburgh, PA (6) Physics, University of Strathclyde, Glasgow, UK

Purpose: (1) To evaluate feasibility and safety of restoration of central vision in patients with atrophic age-related macular degeneration using a wireless photovoltaic subretinal implant. (2) To present path forward to smaller pixels.

Methods: A prospective study in 5 patients with visual acuity ≤20/400 due to geographic atrophy of at least 3 optic discs diameters and no foveal perception. The wireless photovoltaic chip (PRIMA, Pixium Vision) is 2x2mm in size, 30μm in thickness, containing 378 pixels of 100μm in width. In RCS rats, arrays of 1 mm in size with 75 and 55 μm pixels have been tested. Each pixel in the implant converts pulsed near-infrared light (880nm) projected from video goggles into electric current to stimulate the nearby neurons in the inner nuclear layer of the retina.

Results: In all patients, chip was successfully implanted under the macula and remains stable, with a follow-up exceeding 12 months in the first patient. In 3 patients, chip was placed into a desired position - centrally and close to the inner retina. In 2 patients the implant ended up in suboptimal positions – one in the choroid and another off-center. All 5 patients perceive white-yellow patterns with adjustable brightness, in retinotopically correct locations within previous scotomata. No decrease in natural visual acuity was observed in any of the patients. All 4 patients with subretinal placement of the chip correctly identify bar orientation, with 93.5+/-3.8% accuracy, with a minimum bar width of single pixel. Out of them, all 3 patients with central placement of the implant demonstrated visual acuity with Landolt C test in the range of 20/460 - 20/550, which is just 10-30% below the theoretical resolution limit for this pixel size (20/420). Grating visual acuity measurements with 75 and 55μm pixels in RCS rats confirmed that spatial resolution matches the sampling density limit.

Conclusions: Wireless chip PRIMA can be safely implanted under the atrophic macula in patients with geographic atrophy and restore central visual perception with acuity close to the theoretical limit of the implant. Implantation did not reduce the natural residual visual acuity of the patients. Implants with smaller pixels are being developed, including 3-dimensional configurations, aiming to reduce the pixel size down to 20 μm.

Biography: Daniel Palanker is a Professor of Ophthalmology and Director of the Hansen Experimental Physics Laboratory at Stanford University. He received MSc 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, these studies include laser-tissue interactions with applications to ocular therapy and surgery, and interferometric imaging of neural signals. In the field of electro-neural interfaces, he is developing high-resolution photovoltaic retinal prosthesis for restoration of sight, and implants for electronic control of secretory glands and blood vessels.

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

Please describe the new research you plan to present (100 words):

We evaluated feasibility and safety of restoration of central vision in 5 patients with atrophic age-related macular degeneration using a wireless photovoltaic subretinal implant. All patients perceive white-yellow patterns with adjustable brightness, in retinotopically correct locations within previous scotomata. All 3 patients with central placement of the implant demonstrated visual acuity with Landolt C test in the range of 20/460 - 20/550, which is just 10-30% below the theoretical resolution limit (20/420) for this pixel size (100 μm). Implantation did not reduce the natural residual visual acuity of the patients. We will also describe perspectives of development smaller 2-D and 3-D pixels.

Please present a summary (300-word maximum) of the major past and present achievements and contributions of your consortium to the field of artificial vision:

We developed a photovoltaic subretinal prosthesis which converts light into pulsed electric current, stimulating the nearby inner retinal neurons. Visual information is projected onto the retina from video goggles using pulsed near-infrared (880nm) light. This design avoids the use of bulky electronics and wiring, thereby greatly reducing the surgical complexity. Optical activation of the photovoltaic pixels allows scaling the implants to thousands of electrodes.

In ex-vivo studies with rodent retinas, we found dynamic range of selective activation of the inner retinal neurons and created its computational model, which allows optimization of the pixel design. We also demonstrated that retinal response to prosthetic stimulation with subretinal implants preserves many features of natural vision, including flicker fusion at high frequencies (>20 Hz), adaptation to static images, antagonistic center-surround organization and non-linear summation of subunits in receptive fields, providing high spatial resolution.

Our in-vivo studies in RCS rats revealed the dynamic range, contrast sensitivity and spatial resolution of prosthetic vision, which can reach the sampling density limit with 75μm and 55μm pixels.
The clinical trial with our implants (PRIMA, Pixium Vision) demonstrated feasibility and safety of this approach to restoration of central vision in patients with atrophic AMD, with the best visual acuity closely matching the 100μm pixel size limit (20/420).

We also developed 3-dimensional pixel configurations which should enable reducing the pixel size down to 20μm. Such arrays may provide visual acuity exceeding 20/100. Ease of implantation of these wireless arrays, combined with high resolution opens the door to highly functional restoration of sight.

All the basic implant development ex-vivo and studies in rodents are performed at Stanford University. The human version of the system is built by Pixium Vision, which also conducts the clinical studies.

Fivos Panetsos, Ph.D.
Computense University of Madrid
Madrid, Spain

A Silk Fibroin Biohybrid Thalamic Visual Neuroprosthesis. First Steps for the Development of the Biohybrid Retina

Fivos Panetsos1,2,3, Nahla Jemni-Damer1,2, Atocha Guedán-Durán1,2, Rocio Fernández-Serra3,4, Rebeca Gallego- Ruiz1,2,4, Paloma Lozano-Picazo4, Daniel González-Nieto3,4,5, José Pérez-Rigueiro3,4,5,6, Francisco Rojo3,4,5,6, Gustavo Guinea3,4,5,6, Milagros Ramos4,5,7, Assunta Virtuoso8, Giovanni Cirillo8, Michele Papa8, Félix Armada- Maresca9
1. Neuro-computing & Neuro-robotics Research Group, Complutense University of Madrid, Spain.
2. Neural Plasticity Research Group, Institute for Health Research San Carlos Clinical Hospital (IdISSC), Madrid, Spain. 3. Silk Biomed SL, Madrid, Spain. 4.Center for Biomedical Technology. Universidad Politécnica de Madrid, E-28223 Pozuelo de Alarcón, Spain. 5. Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain. 6.Departamento de Ciencia de Materiales, ETSI de Caminos, Canales y Puertos. Universidad Politécnica de Madrid,
E-28040 Madrid, Spain. 7.Departamento de Tecnología Fotónica y Bioingeniería, Escuela Técnica Superior de Ingenieros de Telecomunicación, Universidad Politécnica de Madrid, Madrid, Spain.
8. Division of Human Anatomy – Neuronal Networks Morphology Lab, Department of Mental, Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy.
9.0 phthalmology Service, La Paz University Hospital, Madrid, Spain.

Purpose: Our final purpose is the realization of a biohybrid prosthesis, based on silk fibroin (SF), graphene and cells, to replace the visual tract from the retina to the lateral geniculate nucleus of the visual thalamus (VISNE-Visual Neuroprostheses) project. The first technical objectives are

- Building 3D layered SF biohybrid structures
- In vitro development of 3D layered retinal structures
- In vivo test of 3D layered retinal structures

Here we present 1) 3D layered SF+stem cells biohybrids and their in vivo tests; 2) in vitro-built SF biohybrids of retinal pigment epithelium cells, endothelial cells, and photoreceptors and their in vivo tests.

Methods: Layered biohybrid structures were built with mesenchymal stem cells (mSCs) embedded in a natural SF hydrogel. SF was extracted from Bombyx mori cocoons. Hydrogels geled at room temperature and tested, SF concentration was assessed. PBS was used for the 1st and 3rd layer and DMEM for the 2nd. Approx 4x104 FSE stained bone marrow mSCs from CD1 wild-type mice were included in the DMEM gel. Hybrids were maintained up to 15 days in vitro with culture medium. Cell organization was tested using fluorescence microscopy. Dead cells were marked with propidium iodide and counted at days 3, 7 and 15 under fluorescence microscopy. Functionality of the embedded cells was verified by testing their secretome with ELISA. In vivo biocompatibility and cell survival was tested by implanting hybrids in mice cerebral cortex. 2-10 days after implanting, animals where perfused, brains were extracted, cut into coronal sections and observed under a fluorescence microscope. Artificial retina support was designed and characterized. For the layered structure cultured cells were embedded in SF hydrogels. Biohybrids were kept in vitro 15 days to promote maturation. Cell organization was tested by fluorescence microscopy. Biocompatibility, cell survival and growth capacity were evaluated by haematoxylineosin and calcein/propidium iodide at 2-15 days. Cells' functionality was verified by secretome testing with ELISA and by Fluo-4 AM. Cell viability and proliferation was studied with Ki67. Artificial retinas were implanted in the subretinal space of rats. 30 days later rats were perfused, eyes extracted and the brains, were cut and observed under a fluorescence microscope.

Biography: Fivos Panetsos was born in Athens, Greece. He has a degree in Applied Mathematics from the University of Pavia, Italy and a Specialization in Artificial Intelligence from the Polytechnic University of Madrid, Spain. He is PhD in Biology from the Complutense University of Madrid, Spain and Ph.D. in Medicine & Surgery from the Autonomous University of Madrid, Spain. Fivos Panetsos is Professor at the Faculty of Optics and Optometry of the Complutense University of Madrid, Founder and Director of the Neuro-computing and Neuro-robotics Research Group at the same University and Founder and Director of the Neural Plasticity Research Group at the Institute for Health Research, San Carlos Clinical Hospital of Madrid, Spain. His interests include sensory neural prostheses, biomaterials for neural regeneration and repair, neural plasticity and information processing.

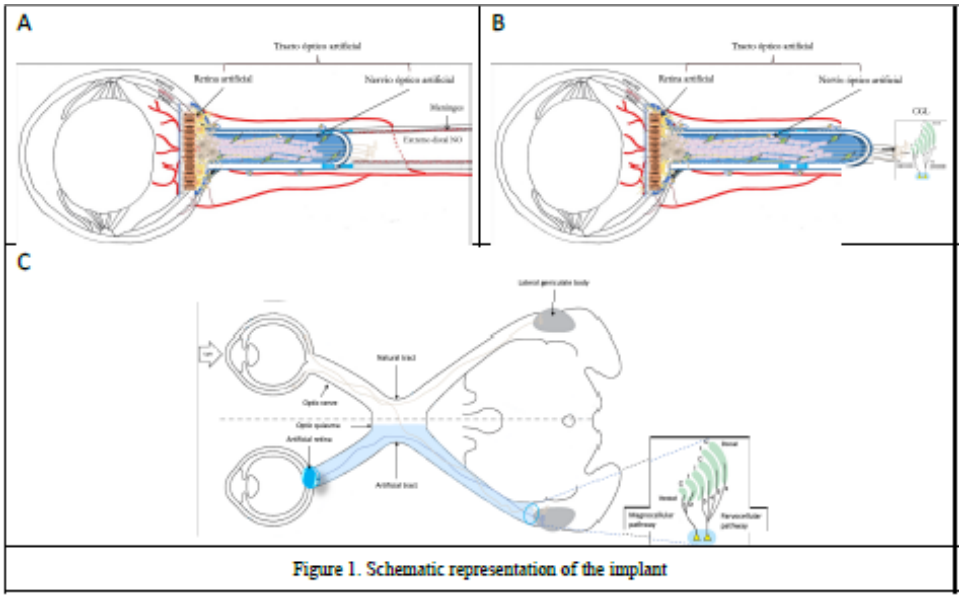


Figure 1. Schematic representation of the implant

Results

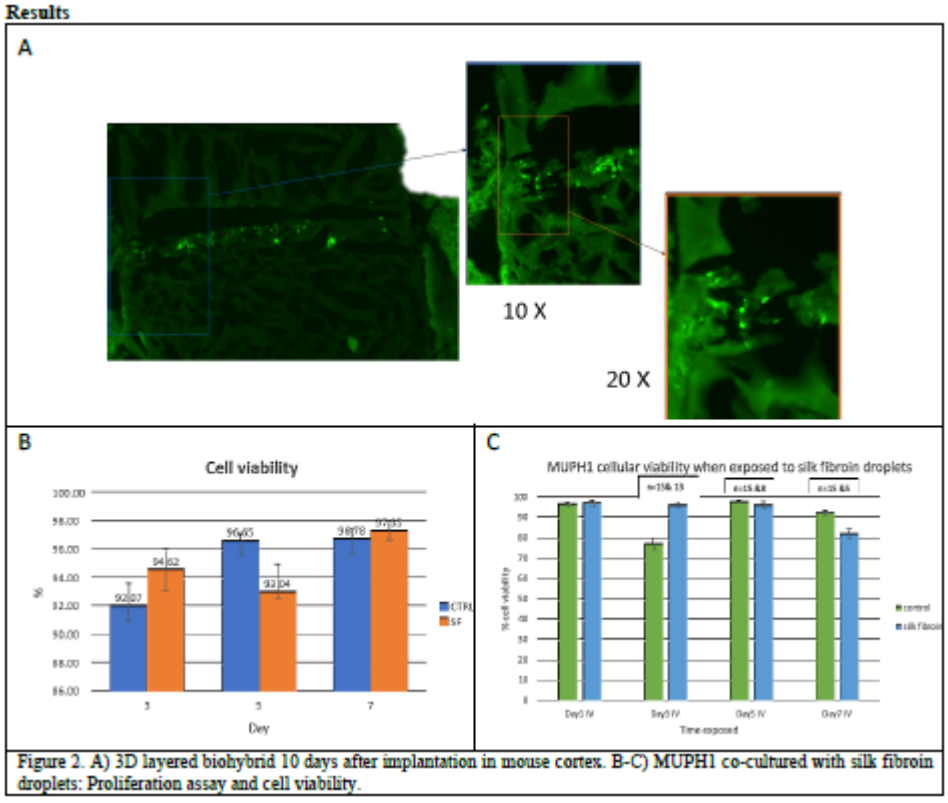


Figure 2. A) 3D layered biohybrid 10 days after implantation in mouse cortex. B-C) MUPH1 co-cultured with silk fibroin droplets: Proliferation assay and cell viability.

Matthew Petoe, Ph.D.
Bionic Vision Technologies
East Melbourne, Australia

The Bionic Vision Technologies Suprachoroidal Retinal Prosthesis: Interim Clinical Trial Results

Matthew A. Petoe1,2; Samuel A. Titchener1,2; Jessica Kvansakul1,2; Mohit N. Shivdasani3,1; D.A.X. Nayagam1,4; Stephanie B. Epp1; Joel Villalobos1,2; Nicholas C. Sinclair1,2; Chris, E. Williams1,2; Nick Barnes5,6; Janine G. Walker5; Jeremy Oorloff5; Nariman Habili5; William G. Kentler7; Robert J. Briggs8; Maria Kolic9; Elizabeth, K. Baglin9; Myra B. McGuinness9; Kiera A. Young9; Carla J. Abbott9,10; Lauren N. Ayton9,10,11; Rosie C.H. Dawkins9,10; Jonathan Yeoh9,10; Danny Chiu9,10; Chi D. Luu9,10; Penelope J. Allen9,10 1 Bionics Institute, East Melbourne, VIC, Australia 2 Medical Bionics Department, University of Melbourne, Melbourne, VIC, Australia 3 Graduate School of Biomedical Engineering, The University of New South Wales, Kensington, NSW 2033, Australia 4 Department of Pathology, University of Melbourne, St. Vincent's Hospital, Victoria 3065, Australia 5 Data61, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Canberra, Australian Capital Territory, Australia 6 Research School of Engineering, Australian National University, Australia 7 Department of Biomedical Engineering, University of Melbourne, Melbourne, VIC, Australia 8 Otolaryngology, Department of Surgery, University of Melbourne, Melbourne, VIC, Australia 9 Centre for Eye Research Australia, Department of Surgery (Ophthalmology), University of Melbourne, Melbourne, VIC, Australia 10 Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, VIC, Australia 11 Department of Optometry and Vision Sciences, University of Melbourne, Australia

Objective: We will present surgical, psychophysical, and functional vision results from the Bionic Vision Technologies (BVT) suprachoroidal retinal implant study in four human subjects with end-stage inherited retinal degeneration (NCT03406416).

Methods: Four patients with end-stage cone-rod or rod-cone dystrophy (retinitis pigmentosa) and perception of light visual acuity were implanted with a 44-channel suprachoroidal retinal implant during 2018. Post-surgical outcomes were assessed routinely using fundus photography and optical coherence tomography (OCT) to visualize the location and orientation of the implant with respect to the optic nerve head, fovea, and posterior surface of the retina. Following recovery and device switch-on, functional vision was characterized using psychophysical evaluation, screen-based tasks, table-top search, and mobility tasks. Participants routinely completed a questionnaire on device usage in daily life, and provided ongoing self-report on their unsupervised device use.

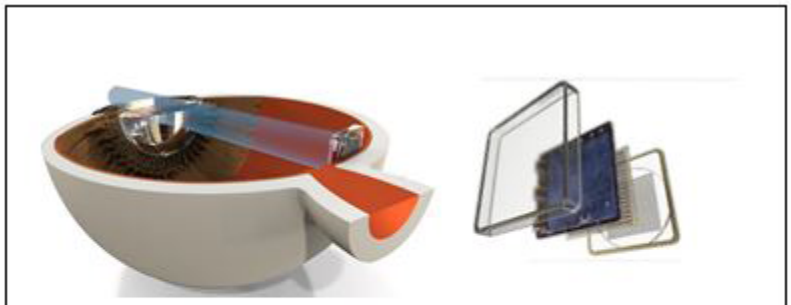
Results: Implantation surgery took between 204 and 260 minutes and was uncomplicated. Post-operative assessments confirmed the absence of retinal trauma and correct device positioning. Recovery was uneventful for all participants and was followed by successful device switch-on between 6 and 8 weeks post-surgery. All participants demonstrated a consistent and significant benefit of the Device On localization tasks and basic orientation and mobility tasks at 20 weeks post switch-on. Average pointing error on a square-finding task was 10.5 ± 5.0° (On) versus 28.3 ± 6.8° (Off) from the center of a 10° wide square. Average pointing error on a table-top search task was 6.2 ± 3.3 cm (On) versus 32.8 ± 11.0 cm (Off). Three participants could discriminate the direction of a moving bar at speeds ranging from 7 to 30 degrees per second. Two participants have a measurable grating acuity, exceeding 0.033 cycles-per-degree. Performance on a door-finding task and an obstacle avoidance task was significantly better for all participants with Device On versus Device Off. Responses to questionnaires on unsupervised experience were graded as overall 'positive' by an impartial examiner.

Conclusion: The BVT suprachoroidal retinal implant can be safely implanted with no retinal trauma or serious adverse events. The device provides functional vision to all participants and positive effect on self-report.

Biography: Dr Petoe's primary fields of research are Signal Processing and Biomedical Engineering, with a focus on human perception, neuroscience, and neurophysiology. He completed a Ph.D. in 2011 at the University of Queensland (which received a Dean's Award for Research Higher Degree Excellence). His first postdoctoral position was as Stroke Foundation Research Fellow in the Neurology Research Unit, Auckland City Hospital, working on novel methods for enhancing plastic changes in the motor cortex of recovering stroke patients. He joined the bionic eye project at The Bionics Institute of Australia in 2012 and was responsible for integrating a video-camera and customising the stimulation strategy used with Bionic Vision Australia bionic eye patients. He is now Team Leader of the psychophysics program and a chief investigator on a trial of safety and efficacy for the Bionic Vision Technologies bionic eye. Dr Petoe holds honorary research positions at the Royal Victorian Eye and Ear Hospital and the University of Melbourne, Australia.

Steven Prawer, Ph.D.
University of Melbourne
Parkville, VIC, Australia

The Diamond Eye: Architecture and Reduction to Practice



The Diamond Eye. Left: All optical power and data link to an epiretinal implant with 288 independently addressable electrodes. Right: Components of the diamond eye: diamond electrode array, ASIC, photovoltaic cell and transparent diamond cap.

Purpose: Retinal implants restore a sense of vision for a growing number of users worldwide. Nevertheless, visual acuities provided by the current generation of devices are low. The quantity of information transferable to the retina using existing implant technologies is limited, far below receptor cells' capabilities. Many agree that increasing the information density deliverable by a retinal prosthesis requires devices with stimulation electrodes that are both dense and numerous. This work describes a new generation of retinal prostheses capable of upscaling the information density conveyable to the retina. Centered on engineered diamond materials, the implant is very well tolerated and long-term stable in the eye's unique physiological environment and capable of delivering highly versatile stimulation waveforms – both key attributes in providing useful vision. Delivery of high-density information, close to the retina with the flexibility to alter stimulation parameters in situ provides the best chance for success in providing high acuity prosthetic vision.

Results: The architecture exploits the latest developments in high efficiency photovoltaic materials to allow for all optical power and data communication with the implant, thus eliminating the need for wires that cross the eye wall. This greatly simplifies the surgical technique for insertion of the device, and allows for more precise epiretinal positioning of the electrodes close to the target ganglion cells. We provide an overview of the latest results on (i) the surgical technique in cadaver eyes, (ii) the efficacy of the wireless laser power and data scheme, (iii) the development of the Application Specific Integrated Circuit optimized for low power operation, whilst maintaining flexibility of stimulation of all 288 electrodes and (iv) initial results on the ability of diamond electrodes to deliver localized stimulation to ganglion cells in explanted retina.

Conclusion: Control of an epiretinal implant using light alone allows for simplification of the surgery, and lowers the risk of complications. When coupled with a highly flexible ASIC capable of independent stimulation of 288 electrodes, and evidence that the spread of activation of the ganglion cells can be contained via the use of short pulses, there is now firm evidence to suggest that this approach is sufficiently promising to proceed to first in human trials.

Biography: Steven Prawer is Professor of Physics at the University of Melbourne and the lead inventor of the Diamond Eye™ and Cofounder of iBIONICS and Carbon Cybernetics. He envisions technology development to benefit health and quality of life by providing a platform to communicate to the brain. He has also led the Melbourne Materials Institute, a multidisciplinary research initiative using advanced material science and technology to address problems of global significance. Professor Prawer has a worldwide reputation in advanced diamond science and technology, has published more than 300 scientific papers. He has received numerous fellowships and awards and in 2010 was elected to the Australian Academy of Science.

Daniel Rathbun, Ph.D.
Henry Ford Health System
Detroit, Michigan

MEA-Based Classification of Retinal Ganglion Cells for Bionic Vision

Hamed Shabani, Mahdi Sadeghi, Zohreh Hosseinzadeh, Eberhart Zrenner, Daniel Rathbun
Purpose: Although there has been significant progress in developing retina implants during last two decades, due to the inability to selectively stimulate different Retina Ganglion Cell (RGC) types, visual perception for retina implant patients remains limited. We hypothesize that different types of RGCs can be selectively activated by deriving stimuli from their different electrical input filters. The input filters of cells are extracted from their response to electrical noise stimulation using the Spike Triggered Averaging (STA) method. To begin testing this hypothesis, we first classify RGC types using a set of visual stimuli and then examine the properties of each cell type's electrical input filters.

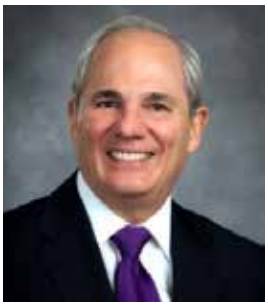
Method: In this study we used the data recorded from nine dark adapted retinas of seven adult wild type mice. A 60 channel microelectrode array in contact with the ganglion cell side of the retina was used to record the spiking neural activity of RGCs. The visual stimulation set was adapted from Baden et al. (Nature 2016), including moving bars, contrast and temporal frequency chirps, blue-green color flashes, and spatiotemporal white noise. In order to extract electrical input filters, a sequence of filtered and interpolated Gaussian white noise voltage steps was used. Similar to Baden et al. we used sparse principle component analysis (sPCA) to extract response features to the visual stimuli.

After projecting data into a lower-dimensional space, we assigned each neuron to one of the 75 clusters reported by Baden et al., by finding the highest correlation between a neuron's response and the clustered response data provided by Baden et al.

Results: We recorded visual responses from 426 RGCs. These responses mapped onto about half of the previously described clusters. Despite convolving our spike trains with a filter to create pseudo-calcium traces for correlation with the previous dataset, many of our responses were significantly more transient than previously reported. ON and OFF cells had different electrical input filters as we have previously reported.

Discussion: Adaptation of the Baden et al. methodology for spike trains instead of calcium recordings was partially successful. For better classification results, new cluster definitions should be derived from a large spike train data set. Electrical input filters do appear to vary with RGC type, but more precise cluster definitions are needed to refine this result.

Biography: Dr. Rathbun received degrees in Neuroscience from the University of Texas at Dallas and the University of California, Davis. He studied bionic vision for a decade in Germany under Professor Eberhart Zrenner, a legend in the field. There, he founded the Experimental Retinal Prosthetics Group at the University Eye Clinic of Tuebingen. In late 2018, Dr. Rathbun moved to Detroit to create the Bionics and Vision lab at Henry Ford where he is an Associate Scientist. He studies the language that the eye speaks to the brain to improve prosthetic vision devices. Such devices restore sight to patients blinded by retinal degenerations such as retinitis pigmentosa and macular degeneration. Dr. Rathbun's research applies the study of neural coding in the visual system to: 1) understanding how images are processed in the healthy and degenerating retina; 2) understanding how the retina responds to electrical stimulation; and 3) using this knowledge to advance bionic vision. At Henry Ford, he is establishing the world's first electrophysiology laboratory dedicated to working with human retinal tissue freshly donated by ophthalmology patients.



Joseph R. Rizzo, M.D.
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

"The Field of Visual Prosthetics: Existential Crisis, or Unrealized Opportunities?"

The field of retinal prosthesis was founded by two independent groups in the late 1980s following earlier explorations of a cortical-based device that were not successful. The opportunity to consider use of a retinal device was enabled by the rapid growth and expertise of the microtechnology industry, which made it possible to consider developing sophisticated microelectronics that could fit into the eye, where they had the potential to treat blinding conditions caused by outer retinal disease. Over the ensuing two decades, more than 20 groups worldwide entered the field of visual prosthetics and developed additional novel technical approaches and notable devices designed for implantation at one of multiple levels within the afferent visual pathway. Important examples of success in our field are numerous and include: 1) chronic human implants being performed on four continents (plus Japan); 2) three groups having received regulatory approval to commercialize their device in either Europe or the United States, or both; 3) Medicare for approval payment for retinal prosthetics in the United States; and 4) one company that trades its stock on the public exchange in the United States. These major milestones understandably have energized researchers and potential patients with the hope that visual restoration for the blind would become a reality. But, recently, the two companies with the most experience in human implantations have effectively shuttered their operations. These corporate experiences have contributed to a third company with decades in the field being at a financial precipice. There remains substantial hope for the type of clinical success that the field has longed for, especially given impressive technologies of other retinal and cortical initiatives that are transitioning through the process of regulatory approval. But, the misaligned priorities that drive the scientific and medical goals vs. those of the financial industry are threatening the existence of our field and the potential for a historic medical breakthrough. This talk will review the technical aspects of our field and the results from human testing, and how these two factors influence the potential for robust and multi-pronged corporate investment, which is necessary for the long-term success of our field and the realization of our commitment to restore vision to the blind.

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.

Nishal Shah
Stanford University
Stanford, California

Temporal Dithering of Epiretinal Stimulation to Optimize Artificial Vision

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Objective: To achieve a breakthrough in artificial vision, it will likely be necessary to accurately replicate the neural code, at least to a degree, in the diverse RGC types. However, because RGCs of different types are spatially intermixed, even high-resolution stimulation may exhibit imperfect selectivity. We propose to optimize device function using a closed-loop approach that calibrates neural responses to a limited set of electrical stimulation patterns, then optimizes stimulation for each incoming visual image in real time.

Methods: Epiretinal recording and stimulation in isolated primate retina with a high-density, large-scale electrode array was used as a lab prototype of a future device. To avoid modeling the complex dependence of cellular activation on arbitrary stimulation patterns, a small 'dictionary' of single-electrode stimulation patterns was used, and the probability of neural response measured empirically by repeated stimulation. To optimize the artificial visual image, a rapid sequence of dictionary elements was delivered, progressively assembling the image within an assumed visual integration time of tens of milliseconds. Greedy selection of the stimulation sequence from the dictionary, sequentially minimizing the mean-squared error between the visual stimulus and a linear reconstruction of it (as a surrogate for perception), yielded a real-time algorithm.

Results: For static white noise images, a large improvement in performance was observed compared to existing approaches – specifically, an error increment of 3% relative to an optimal algorithm for the single-electrode dictionary, and 10% relative to a device that perfectly controls neural response. By comparison, stimulating according to image intensity without reference to cell type, as is done in present-day devices, produced error increments of 40% and 50% respectively. Similar results were obtained using a spatio-temporal linear decoder and naturalistic images with simulated eye movements. Using only the most effective 50% of electrodes minimally affected performance, suggesting that an adaptive, calibrated device may permit significant reductions in power consumption.

Conclusions: Temporally dithering stimulation patterns produces a substantial improvement in performance relative to traditional mapping of image pixels to electrodes. The framework can also be used to evaluate and optimize performance with different stimulation dictionaries and hardware configurations.

Biography: Nishal Shah is a PhD student in Electrical Engineering at Stanford, advised by Prof. EJ Chichilnisky. He uses ex-vivo multi-electrode recordings to build algorithms for characterizing the electrical and visual response properties in the retina, and uses this for converting the visual input to electrical currents in real time. Previously, he was a student researcher at Google Brain and finished Bachelors and Masters from IIT Delhi.

Martin J. Spencer Ph.D.
Bionic Vision Technologies
East Melbourne, Australia

Experimentally Constrained Predictions of the Efficacy of a Global Activity Shaping Strategy

Martin J. Spencer1, Tatiana Kameneva1,2, David B. Grayden1, Hamish Meffin3,4, Anthony N. Burkitt1
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2. Faculty of Science, Engineering and Technology, Swinburne University of Technology, Hawthorn, Victoria, Australia
3. Department of Optometry and Vision Science, The University of Melbourne, Parkville, Victoria, Australia
4. National Vision Research Institute, Australian College of Optometry, Carlton, Victoria, Australia

Purpose: Electrical stimulation inevitably entails some lateral spread of current within the target neural tissue (Wilke et al. 2011). This leads to implicit limits on the useful electrode density when using a conventional stimulation strategy. A global activity shaping strategy provides a method to overcome this limitation. The approach assumes a forward model to convert a set of electrode amplitudes, s µinto a pattern of neural activity, r µ(Spencer et al. 2019),

r~=g(Ws)µ

where **W** is a matrix giving the magnitude of the current at each retinal location resulting from the activation of each electrode, and g() is a nonlinear function to calculate the neural activity. The approach inverts this model to convert a desired pattern of neural activity, r µ̂*, into the electrode amplitudes required to generate this desired pattern.

Here we validate these forward and inverse models using in vivo cortical data.

Method: In vivo experiments were carried out in cats with a stimulation array implanted in the retina (6×7 electrodes) while recordings were made in cortical area V1 (6×10 electrodes). 3600 trials of white noise stimulation/recording pairs were split randomly into two groups of 1800 used to calculate a forward model and inverse model. The inverse model was used to calculate a set of stimulation patterns, while the forward model was used to predict the expected results of applying these patterns.

Results: Two approaches to calculate the inverse model were compared: a simple pseudoinverse of the matrix W and a quadratic programming approach, which places explicit limits on the electrode amplitudes. In both approaches singular value decomposition was used with eigenvalue selection to calculate the pseudoinverse of the matrix W. To determine optimum number of eigenvalues to use, the mean squared error (MSE) was measured: a low number of eigenvalues resulted in high MSE due to low resolution, whereas a high number of eigenvalues resulted in a high MSE due to overfitting (Figure 1).

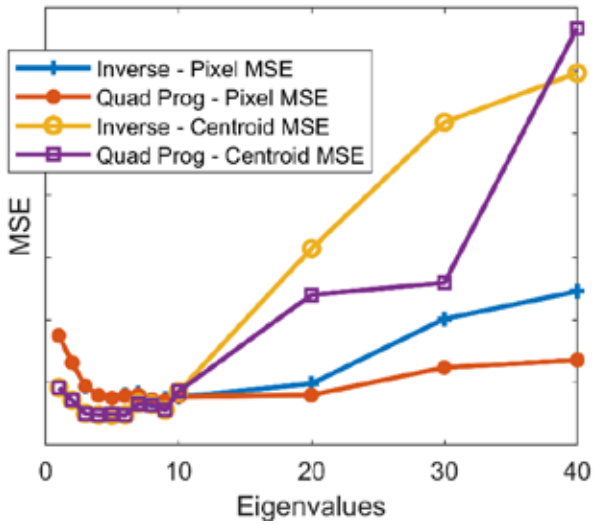

Figure 1: The results of using the pure pseudoinverse approach and a quadratic programming approach. The error was measured either as a pixel by pixel MSE or as the difference in the position of neural activity (arbitrary units).

Conclusion: Using an experimentally constrained forward model, a method for determining a global activity shaping algorithm is presented, which is shown to be optimised by careful selection of eigenvalues to avoid over-fitting.

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 BSc 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.

Steven Stasheff, M.D., Ph.D.
National Institutes of Health
National Eye Institute
Bethesda, Maryland

Expanding the Restorative Capacity of Visual Prostheses Beyond Retinal Diseases: Neurofibromatosis as an Iconic Example

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PURPOSE: The development of electronic visual prostheses accelerated during the past few decades, culminating in clinical trials and governmental approval of several commercially available retinal prostheses. This firmly established proof of principle that long-term electronic implants can restore basic visual perception to patients with specific retinal disorders. As alluded by Dr. Hessburg's recent letter to the visual prosthesis research community, it is appropriate now to emphasize prosthesis designs that restore vision in a broader range of blinding diseases than those with primarily retinal pathology.

METHODS: Beginning with neurofibromatosis type 1 as a central example, I will summarize recent findings from our own studies of a mouse model targeting neurofibromin (Nf1) mutations to developing glia, in which we assessed visual behavior (optomotor responses [OMR]), in vivo anatomy (optical coherence tomography [OCT]), in vitro multielectrode recording of spontaneous and light-evoked RGC activity, and histologic analysis of RGCs, optic nerves and chiasms. Some of these results were quite unexpected and are not addressed by current visual prosthesis designs. I also will review other sight-depriving disorders with disparate but similarly complex challenges.

RESULTS: Highlighted findings include elevated spontaneous and abnormal light-evoked activity of retinal ganglion cells (RGCs), hypomyelination or destruction of RGC axons in the optic nerves, alterations in projections of RGCs to central nervous system (CNS) targets, abnormal glial development and interactions with neurons, and altered visual processing in the retina and downstream central visual system structures. I compare the impact of these factors on the promise of electrical stimulation to restore vision vs. alternative approaches such as gene therapy, stem cell or tissue transplantation, or the expanding range of assistive technologies (e.g., cell phone apps, artificial intelligence (AI), visual augmentation goggles).

CONCLUSIONS: These aspects of sight-depriving diseases highlight the need for the next generation of visual prostheses to benefit a broader range of visual disorders. I encourage conference participants to discuss: 1) visual cortical stimulation; 2) increased flexibility to "re-program" systems for varied diseases and subjects, and as diseases wax and wane over time; 3) enhancing, rather than replacing, limited residual vision; and 4) incorporating AI to refine stimulation.

Biography: Steven F. Stasheff, MD, PhD is an Attending Pediatric Neuro-ophthalmologist at Children's National Medical Center (CNMC) and the Gilbert Family Neurofibromatosis Institute (GFNI), and Assistant Professor of Pediatrics (Neurology) at the George Washington University. He is a Guest Researcher in the Unit on Retinal Neurophysiology at the National Eye Institute, National Institutes of Health, closely coordinating his basic research with CNMC and the GFNI. He obtained his B.A. in Biology and Physics from the University of North Carolina – Chapel Hill, his MD & PhD in Pharmacology at Duke University, and completed clinical training in Pediatrics, Pediatric Neurology, and Neuro-ophthalmology at Children's Hospital of Philadelphia and Children's Hospital-Boston. He conducted a post-doctoral research fellowship under Richard Masland before joining the Institute for Vision Research at the University of Iowa prior to his current position.

Research interests of his laboratory center on the fundamental physiologic mechanisms of neurologic diseases affecting the visual system, and on the role that central nervous system (CNS) plasticity may play in both the pathogenesis and potential treatments for such disorders. His earlier investigations aimed to better understand electrophysiologic changes that occur in hereditary retinal degeneration, particularly its congenital and early childhood forms, particularly the role that developmental plasticity plays in resculpting specific inner retinal circuits, a field that has continued to grow as summarized in a Frontiers Research Topic he co-edited with Enrica Strettoi, PhD (https://www.frontiersin.org/research-topics/3557/disruptions-of-visual-processing-by-the-inner-retina-accompanying-photoreceptor-degenerations#overview).

The major thrust of ongoing investigations is to help resolve a striking mystery confounding the care of young children with neurofibromatosis type 1 (NF1): why the visual loss suffered by many patients with NF1 and optic pathway gliomas (OPGs) does not correlate tightly with tumor characteristics – that is, structure does not accurately predict function. Dr. Stasheff uses multiple methods including behavioral, in vivo and in vitro anatomy and electrophysiology to address this question in genetically engineered mice. He also collaborates with other NEI investigators to understand how neuroprotective mechanisms in hibernating ground squirrels may be translated to improve recovery from traumatic brain injury (TBI) or other neurologic injury.

Alfred Stett, M.D.
Okuvision GmH
Reutlingen, Germany

Biography: Alfred Stett has been the CEO of Okuvision Reutlingen, Germany, since 2019. From 2017 to 2019 he was an Executive Board Member and CTO of Retina Implant AG, Reutlingen, Germany. From 2008 to 2017 he was the Deputy Managing Director of the Natural and Medical Sciences Institute (NMI) at the University of Tuebingen, Germany. He studied Physics at the University of Ulm, Germany, where he received his doctorate degree in 1995 for his research in the field of electrical stimulation. In 1996 he joined the University Eye Hospital, Tuebingen, and started his research on subretinal implants for blind people. From 1998 to 2017 he has worked at the NMI, where he led several R&D projects in the fields of neuroprosthetics and electrophysiology.

Vernon Towle, Ph.D.
Illinois Institute of Technology
Chicago, Illinois

The Color Option

Vernon L. Towle, Tuan Pham, Michael McCaffrey, Anqi Jiang and Philip R. Troyk, The University of Chicago and Illinois Institute of Technology

Purpose: All of the human prosthetic visual systems implanted so far have been achromatic. As visual prosthetic systems become more capable, at some point the color option will be implemented. We discuss here software implementation strategies and consider the advantages and disadvantages of a color prosthetic mode.

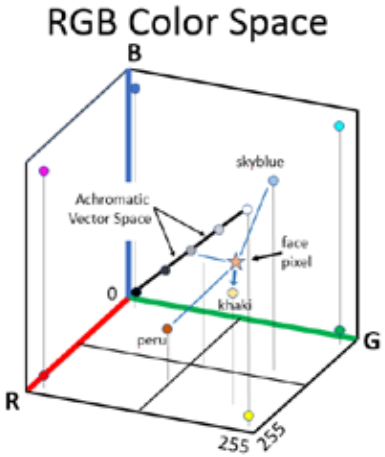


Fig 1. RGB Color Space contains 2563 unique colors. Here, the RGB value of a pixel located over a face (gold star) in the video input frame is closest to the color khaki, similar to some skin colors.

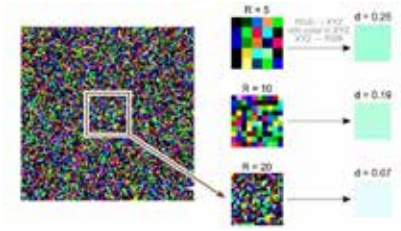


Fig 2. Hypothetical 2D cortical color selectivity map (100 x 100) with each pixel's selectivity sampled uniformly from the RGB color space. Increased recruited activation size (R = 5, 10, 20) leads to increased desaturation (d, the Euclidean distance to the achromatic vector).

Background: Penfield & Rasmussen (1950) reported that 75% of 134 occipital stimulations revealed phosphene with color characteristics, with 52% of phosphenes described as being a single color. Schmidt et al. (1995) reported that at low stimulation intensities phosphenes usually had a specific hue, but when the stimulus intensity was increased, they desaturated to white. We wonder whether previous B/W prosthetic systems were over-stimulating the visual cortex to obtain white phosphenes, which may be why after-discharges and seizures were not an uncommon occurrence.

Method: One strategy to reduce the vast color space of the prosthetic's camera to a handful of subjectively reported phosphene colors is to calculate the squared Euclidean distance of each pixel's RGB value to mapped colors (Fig 1). Once identified, stimulation current for each electrode can be assigned from a color vs. B/W look-up table.

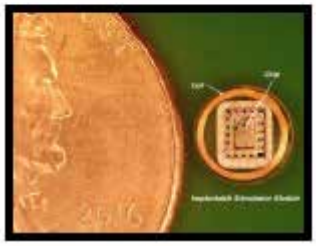
Results: In our simulation of primary visual cortex, increased stimulation currents may activate more color units (R) and lead to increased phosphene desaturation (Fig 2).

Conclusion: Colored phosphenes can be helpful for navigating the natural outdoor environment, locating blue sky, green grass, grey sidewalks, colorful automobiles, and traffic lights. They have the advantage of being elicited by lower levels of stimulation, reducing the probability of causing after-discharges or seizures. On the other hand, they reduce the spatial resolution of the image by the proportion of colors partitioned. This is a serious limitation for the immediate future, where systems will have limited spatial resolution.
However, the ability to temporarily switch to a color mode when desired could add critical new information to facilitate one's visual perception. Alternatively, such a "color" mode would not have to necessarily duplicate actual color of physical objects as defined by the camera. For example, a visual pattern recognition system that recognizes moving cars, or nearby obstacles to ambulation, could encode the phosphenes that define such things to be red, thus providing an enhanced dimension of visual perception for the user.

Biography: Dr. Towle is a Professor of Neurology and Neurosurgery at the University of Chicago, and is a member of The Grossman Institute for Neuroscience, Quantitative Biology and Human Behavior, The Committee on Computational Neuroscience, and The Committee on Neurobiology. His research interests are broad, and include human visual psychophysics, clinical neurophysiology, epilepsy, electrocorticography, color vision, cortical visual prostheses, and the history of science. He is part of an ongoing NIH grant addressed at determining the safety and efficacy of an intracortical visual prosthesis awarded to The Illinois Institute of Technology. He obtained his B.A. at The University of California at Davis, M.A. at California State University at Sacramento, and Ph.D. at The University of North Carolina at Greensboro, followed by post-doctoral training in ophthalmology at Tufts-New England Medical Center and cognitive neurophysiology at The University of Illinois.

Philip R. Troyk, Ph.D
Illinois Institute of Technology
Chicago, Illinois

Intracortical Visual Prosthesis (Icvp): Progess Towards the Clinical Trial



Purpose: Funded under the BRAIN Initiative, the Illinois Institute of Technology (IIT) is completing the second year of a team-based 5-year project for a clinical trial of the IntraCortical Visual Prosthesis (ICVP. Our team has researchers from seven institutions: Illinois Institute of Technology, University of Chicago (UC), University of Texas, Dallas (UTD), Johns Hopkins University (JHU), MicroProbes for Life Science (MLS), Sigenics, Inc, and the Chicago Lighthouse for People who are Blind or Visually Impaired (CLH). Using intracortical electrical stimulation of the human occipital cortex, we are investigating 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. We are presently completing the 2nd project year after which we expect to have FDA and IRB approval for implanting 5 volunteers. Since the WFMA is wireless and untethered, complete dural closure can be used, and there are minimal disruptive forces on the cortical interface. However, owing to the unique design of the WFMA, navigating preclinical testing has been a challenge since most ISO standards are defined for devices that are much larger than the WFMA.

Results: ISO 10993 chemical characterization, biocompatibility, and large animal test results have shown no significant results over controls. Our work over the past five years in multiple animal experiments has shown minimal biological response, and unprecedented neuronal survival near the WFMA electrode tips. Our interactions with the FDA in the Q-sub phase of IDE submission have proved highly-valuable for improving the design of the clinical trial, and the understanding of the likely behaviour of the WFMA once implanted. IEC 60601, and ISO14708 tests have revealed no significant concerns for chronic implantation of the WFMAs. In a preliminary MRI study, the WFMAs appear benign and unaffected. We expect that, following IDE/IRB approval, a first ICVP volunteer will be implanted in 2019.

Conclusions: The ICVP technology major strength is the flexibility of use. The WFMA placement easily conforms to the brain gyri, thus maximizing the use of cortical area. Given the expectation of stability and longevity for the ICVP cortical interface, we expect that long-term artificial visual perception will be investigated in our clinical volunteers, adding valuable knowledge to the intracortical stimulation field for visual prostheses. The "thumbtack"-like nature of the WFMA makes it attractive for other neural interface applications in the periphery and the spinal cord – both of the applications are under investigation.

Biography: Dr. Troyk is a Professor in the Department of Biomedical Engineering, an Associate Dean of the Armour College of Engineering, at IIT, and a Faculty Associate in the Department of Neurosurgery at the University of Chicago. His research interests are broad and include cortical and retinal visual prostheses, implantable EMG sensors (IMES), 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.

Jiayi Zhang, Ph.D.
Fudan University
Shanghai,China

Nanowire Arrays Restore Vision in Blind Mice

The restoration of light response with complex spatiotemporal features in retinal degenerative diseases towards retinal prosthesis has proven to be a considerable challenge over the past decades. Herein, inspired by the structure and function of photoreceptors in retinas, we develop artificial photoreceptors based on gold nanoparticle-decorated titania (Au-TiO2) nanowire arrays, for restoration of visual responses in the blind mice with degenerated photoreceptors. Green, blue and near UV light responses in the retinal ganglion cells (RGCs) are restored with a spatial resolution better than 100 μm. ON responses in RGCs are blocked by glutamatergic antagonists, suggesting functional preservation of the remaining retinal circuits. Moreover, neurons in the primary visual cortex respond to light after subretinal implant of nanowire arrays. Improvement in pupillary light reflex suggests the behavioral recovery of light sensitivity. Our study will shed light on the development of a new generation of optoelectronic toolkits for subretinal prosthetic devices.

Biography: Dr. Jiayi Zhang received her B. Sc. Degree in physics from Hong Kong Baptist University in 2003 and Ph.D. degree from Brown University in 2009. From 2009 to 2011, she was a Brown-Coxe postdoctoral research associate in the Department of Neurobiology at Yale University. She joined Institutes of Brain Science at Fudan University in 2012. She is currently the vice director of State Key Laboratory of Medical Neurobiology and the Assistant Dean of Institutes of Brain Science.

Her recent work focused on the function, restoration and smart technology-interface of vision. Her research is supported by Ministry of Science and Technology, National Science Foundation of China, Shanghai Municipal of Science and Technology and ZL Lab. She is the deputy chairman of the Sensory and Motor Branch of the Chinese Neuroscience Society and deputy chairman of the Youth Working Subcommittee of Chinese Association For Physiological Sciences.

Eberhart Zrenner, M.D.
University of Tuebingen
Tuebingen, Germany

The Challenge to Meet the Expectations of Patients, Ophthalmologists and Public Health Care Systems with Current Retinal Prostheses

E. Zrenner, R. Rubow and A. Stett, (Tübingen/Reutlingen, Germany)

Since 1995 a subretinal implant for blind patients with retinitis pigmentosa has been developed in Germany, first supported by public research funds and as of 2003 by private investors. After 3 clinical trials (Zrenner et al. 2011; Stingl et al. 2015, 2017) the RETINA IMPLANT Alpha AMS with 1600 pixel and approximately 5 years of life time received the CE mark in 2016, was registered as medical device on the market, and reimbursed by the public health care system in Germany. Further centers in UK, France and Italy had started to establish this treatment within their national health care system. Thirty patients have received the RETINA IMPLANT Alpha AMS produced and distributed by Retina Implant AG (Reutlingen, Germany).

Unfortunately, the economic potential achievable with today's electronic retinal implants in the small market of the rare disease retinitis pigmentosa (RP) is not enough for a viable economic perspective. Thus commercial returns were insufficient for the continuation of Retina Implant AG (Reutlingen, Germany). As a result, the development, production and supply to hospitals of Retina Implant Alpha AMS has been discontinued in March 2019 and Retina Implant AG has concluded its business activities. Production of the epiretinal Implant ARGUS II, developed and marketed by Second Sight (Sylmar CA, USA) has been stopped as well, according to press releases. Nevertheless, continuing care for patients who have received retinal implants in recent years will be provided by clinical partners. We see several reasons for such developments:

1. After many clinical studies, numerous implantations and demanding visual training, it is now clear that the expectations of most candidates for electronic implants cannot be met regarding the improvement of visual quality and the associated everyday benefits. Improvements of visual functions by today's retinal implants for handling activities of daily living are considered by most interested patients as too small. Although some patients with Retina Implant Alpha were able to read letters and words (Zrenner et al. 2011) and even identify facial expressions, only a fraction of patients (40%-50%) had some benefit in typical daily living tasks (Stingl 2015, 2017). Preoperatively it cannot be predicted what patients will be the ones who will benefit.

2. Regulatory processes take too long in implementing lab-tested technical improvements into modified devices approved for marketing. Even small modifications require clinical trials with high financial commitments.

3. Achieving coverage of costs for retina implant surgery by health care insurance systems is different and cumbersome in each and every country. Although binding general contracts are in place with the central association of all German public health insurances the individual insurance of the patient hesitates to accept cost coverage for the recommended treatment.

4. Alternative solutions are provided by the rapidly increasing number of convenient and easy to handle smartphone apps that translate visual tasks into information accessible to blind people especially dedicated to daily living tasks.

5. All of the above requires readiness for investors to face relatively high risks – with financial returns not to be expected for many years.

6. Time consumption and complexity of retinal surgery is demanding and needs to be reduced significantly.

PLATFORM SPEAKERS

It has become clear that for continued market success retinal implants need to be improved considerably to meet the expectations of patients, ophthalmologists, investors and health care insurances. Main functional requirements are: larger visual fields, a higher spatial resolution, an improved contrast, and a higher number of simultaneously discernible gray levels, ideally including chromatic information. Equally important are protocols for the electrical stimulation of the degenerating and continuously remodeling retina to provide long-term stable and reliable perceptions throughout the entire visual field. Also a strong focus on the development and reimbursement of appropriate visual rehabilitation techniques is required so that patients can learn more quickly to integrate artificial vision benefits into their daily living which is crucial for the survival of retinal prostheses on the market and for their availability to patients.

Although RETINA IMPLANT Alpha AMS will no longer be available for implantation in man, research for improvements will go on in our labs with preclinical work on more advanced implant models meanwhile already developed.

Biography: Dr. Zrenner is Professor of Ophthalmology at the Institute for Ophthalmic Research at the Centre for Ophthalmology of the University of Tuebingen, Germany. His research interests include: retinal physiology and pathophysiology, neuro-ophthalmology, ophthalmogenetics and retinal prosthesis including a unique electronic subretinal prosthesis with 1600 pixels, a registered medical device in Europe. He has been instrumental in starting and successfully performing the first gene therapy trial worldwide in achromatopsia (CNGA3).

Prof. Zrenner has studied electronic engineering as well as medicine at the Technical University of Munich, where he obtained his MD degree in 1972. Subsequently he worked for 16 years at the Max-Planck-Institute for Physiological and Clinical Research in Bad Nauheim and with a Fogarty fellowship at the National Eye Institute, NIH, Bethesda, MD. After Habilitation he did a residency at the University Eye Hospital in Munich, later on receiving there an associated professorship. He became full professor and Chairman at University Eye Hospital in Tuebingen in 1989, now Center for Ophthalmology. There he founded the Institute for Ophthalmic Research at Tübingen University and has established a special clinic for hereditary retinal degenerations. He was Chairman of the Tuebingen Center for Neurosensory System until March 2018 and has now a Senior Professorship until 2020. He has received numerous grants and awards and has published approximately 530 peer reviewed papers (see home page: http://www.eye-tuebingen.de/zrenner), cited 25.630 times, with an h-Index of 80 (Google Scholar).

Muzaffer Akyürek
Makmems Mikroelektronik,
Konya-TURKEY

Subretinal Prosthesis Design and Production

Purpose: Nanoelectronics and biomimetics approximation enables exciting features of nanoelectrode arrays that extreme miniaturization is possible. The CMOS-NANO integrated circuits designed to obtain low power consumption and increasing the resolution.

Method: The subretinal prosthesis we propose to build use three main part in its construction:

1)Photonic-layer: It has nanowires which have coating a antireflection layer or embedded nanoentities layers other combinations of materials (e.g. Carbon nanotube) that possesses a high optical absorption coefficient in the visible or near-IR Design guidelines are laid down for maximized injection and enhanced absorption of the incident photons. Optical simulations are carried out using FDTD solutions. Results of optical simulations are mapped onto the electrical model of a cell considering the changes in electrical properties of the layer. It is possible to calculate the expected photoelectric current, or the electron-hole generation rate from the results of the FDTD simulation. This information then be used to perform electrical modeling of the device by TCAD applications. We analyzed and showed that efficient than 2D structures. To explain the origin of the strong light absorption in vertical nanowires, we use finite element method (FEM).

2) Readout-layer:
Resistive network investigated to design for performing image processing task with spatial temporal smoothing. Circuits designed with CAD application which is based on 0,18 um, subthreshold MOS design and thin film technology. We analyzed 3D-IC signal integration.

3) Biocompatible (nonreversible reaction between the microelectrode and the solution is not
desired) flexible electrode arrays: Several materials have been investigated for biomedical electrodes. Noble metals such as platinum and iridium are the most common but other materials such as Iridium oxide, Titanium nitride, Tantalum pentaoxide and Carbon (fibers or nanotubes) have also been investigated. Gold can be used for recording. Because extracellular signals are weak, it is important to have low noise microelectrodes. 3D IC bumping will use between circuit and flex electrode arrays. We used pyramidal microstructures for good penetration with retinal tissue.

Results: Preliminary results indicate the nanoelectronics and biomimetics approximation and the CMOS-NANO integrated circuits can be use to obtain low power consumption and increasing the image resolution.

Conclusion: These researches provide opportunities for new approaches. The innovative subretinal prosthesis design offers novel innovative approach to solutions based on new technologies and approaches.

Biography: Muzaffer Akyürek is currently a research and project manager for novel nanoelectronics, nanophotonics in stacked 3D integrated CMOS image sensors, ultra low power mixed signal ASIC design and optical systems design especially for biomedical applications in the Makmems Mikroelektronik. He was R&D engineer in Alcatel and Siemens. He has BSc. Engineering degree.

Michael P. Barry, Ph.D.
Research Scientist
Second Sight
Sylmar, CA

Single-Electrode Phosphene Characteristics of the Orion™ Visual Cortical Prosthesis System

Michael P. Barry1, Michelle Armenta Salas1, Uday Patel1, Soroush Niketeghad2, William Bosking3, Varalakshmi Wuyyuru1, Daniel Yoshor3, Jessy Dorn1, Nader Pouratian2 1Second Sight Medical Products, Inc. 2University of California, Los Angeles, Department of Neurosurgery 3Baylor College of Medicine

Purpose: Evaluate the sizes, shapes, locations, and counts of phosphenes elicited by single electrodes of the Orion™ Visual Cortical Prosthesis System.

Methods: Four blind subjects participated in these experiments. Each subject was implanted with the Orion cortical visual prosthesis between January and May 2018. All stimulating arrays were implanted over the left medial occipital cortex. Principal data were collected 1–2 and 9–12 months after implantation. Subjects sat 30 cm away from a touchscreen monitor, positioned such that the left edge of the monitor was directly in front of the subject's midline. Subjects were asked to fixate on that edge of the touchscreen during stimulation and while responding. For each trial, a 6, 20, or 120 Hz stimulus at 0.8–7.5 mA was provided through a single electrode. After stimulation was complete, the subject drew the perceived phosphenes on the touchscreen. Responses were pooled across subjects, electrodes, and frequencies to calculate summary statistics.

Results: The smallest phosphenes were described as being about 1° in diameter. Point phosphenes and lines were therefore interpreted as being at least 1° wide. Subjects indicated that phosphenes appeared as straight lines, arcs, right angles, squares, circles, and amorphous regions of light. Positions of phosphenes ranged 1–45° in eccentricity, mean 23°, at -82–89° azimuth, with a mean of -13°. Phosphene area significantly correlated with eccentricity (bootstrap resampling, $p < 10\text{-}6$). Areas ranged 0.8–190 degrees2, with a mean of 29 degrees2. Most percepts were described as being single, contiguous phosphenes, but stimulation on approximately 8% of electrodes elicited 2 or 3 percepts.

Conclusions: Single-electrode Orion cortical stimulation induced varying numbers of percepts with wide ranges of sizes and shapes. Some subjects perceived different shapes with different electrodes, but perceived shapes were consistent across trials. Phosphene area tended to increase with eccentricity.

Biography: Michael P. Barry earned his Ph.D. in biomedical engineering from Johns Hopkins University in 2018. He studied under Gislin Dagnelie, Ph.D. starting in 2007, during which time he conducted and published research concerned with simulations of retinal-prosthesis use and the visual function of retinal-prosthesis users. He received the Envision-Atwell Award for low-vision research in 2017. Dr. Barry has collaborated with Second Sight Medical Products, Inc. since 2009 on the Argus® II Retinal Stimulation System Feasibility Study and currently works as a research scientist for the company. His current research focuses on evaluation and development of the Orion® Visual Cortical Prosthesis System. Dr. Barry also served as a consultant on Goldmann visual field analysis with QLT, Inc. in 2012–2014.

Marwan Besrour, Ph.D.
University of Sherbrooke
Quebec, Canada

Artificially Intelligent Gaze Tracking System for Wireless Neurostimulation Retinal Implant

Marwan Besrour, William Lemaire, Maher Benhouria, Gabriel Martin Hardy, Konin Koua, Sébastien Roy, Réjean Fontaine

During the last century, geriatric needs have grown exponentially, and the multidisciplinary field of biomedical implants evolved accordingly. Following the success of cochlear implants, retinal implants emerged as a promising solution to degenerative retinal diseases. Age-related macular degeneration (MD) and Retinitis pigmentosa (RP) are retinal diseases that damage the rods and cones responsible for converting light to electrical stimuli in the neural layers of the retina. In these diseases, the optic nerve and sub-retinal neural layers are unharmed, presenting an opportunity to use microchips to create artificial vision by electrical neurostimulation. Current commercial designs incorporate invasive wires through the scleral wall of the eyeball, thus increasing infection and rejection risks. Therefore, wireless links constitute a natural evolution to provide power and data to the implant. We propose a low-power optical laser to send stimulation patterns and power to a retinal implant.

Consequently, we need an efficient pupil-tracking system to keep the laser constantly aligned. Eye movement can reach a peak velocity of 900 degrees per second corresponding to a linear speed of 0.47 meters per second. Given the implant size of 5 mm x 4 mm, an estimated delay of 10.6 ms suffices to reach total misalignment, whereby no portion of the incident laser light falls on the device. This new proposed optical link poses a new challenge in terms of predicting the pupil position and re-aligning the MEMS mirror to redirect the laser beam accordingly in real-time to maintain continuous stimulation. The bottleneck in the tracking chain will inevitably be pupil detection. Indeed, image processing is known to consume a significant portion of computing time and power, especially on embedded mobile devices where resources are limited.

Classical processor architectures process data in a sequential manner. The CPU reads instructions from the RAM and processes the data accordingly within an Arithmetic & Logic Unit (ALU). We propose to use an Artificial Neural Network for pupil detection. ANNs process data in a parallel configuration which is best suited for image processing. Indeed, an ANN architecture could process the pixels simultaneously, while classical CPUs requires sequential operations, making it theoretically a hundred times slower.

Under the particular time constraints for laser re-alignment, pupil detection is the most time consuming step in the processing chain. Machine Learning (ML) Techniques show great potential for solving image processing computational complexity in low power, mobile computing architectures. This is hitherto the first reported Artificial Neural Network to be physically implemented in a Field Programmable Gate Array (FPGA) for gaze tracking.

Movidus state-of-the-art neural processors integrated on a Google AIY kit for computer vision achieved 370ms inference time for object detection at peak performance with 94% CPU usage. An Artificial Neural Network implemented on an FPGA holds great potential to reduce the inference time, thereby enabling wireless retinal neurostimulation prostheses. The ANN has an input and output layer and two successive hidden layers to increase inference order. The input layer processes each pixel as an independent neuron and the output layer provides the estimated center of the pupil as (X,Y) coordinates. 1 0 1 0 1 DATA

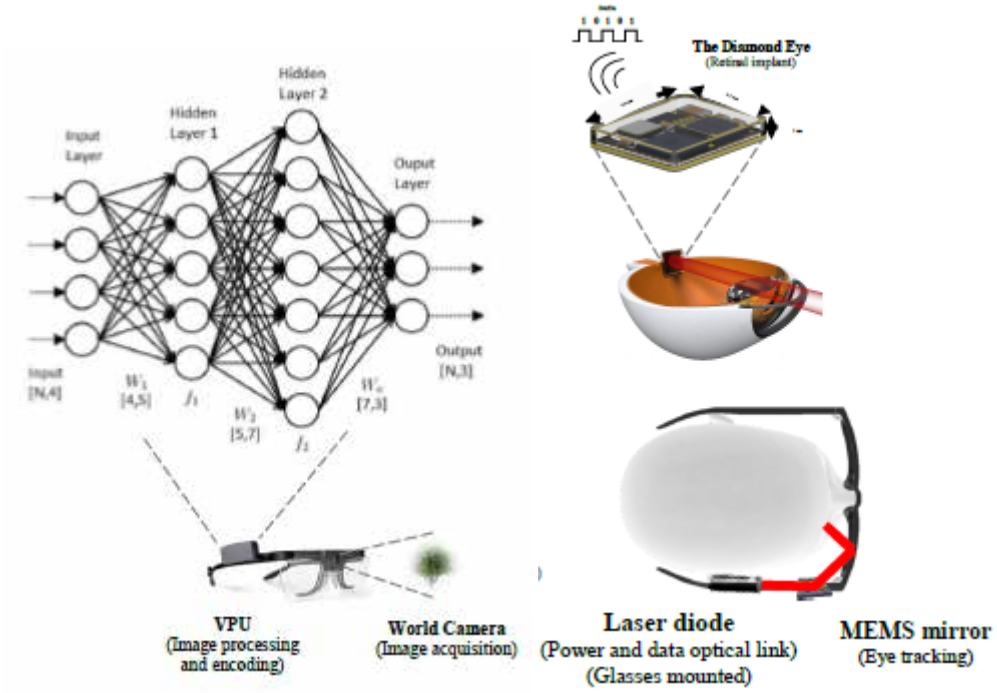


Fig 1: Smart wearables including the ANN processing unit and the MEMS mirror to align the laser

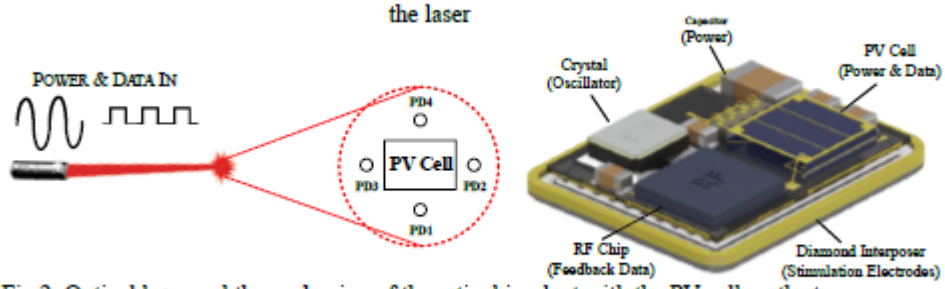


Fig 2: Optical laser and the packaging of the retinal implant with the PV cell on the top

1 mm

Biography: Marwan Besrour is a Ph.D. student in Electrical Engineering at the University of Sherbrooke. Our research group, the GRAMS, works on innovative biomedical implants and scanners. We are currently developing a fully wireless and battery less neurostimulator retinal implant. Our research activities focus on designing a robust wireless full-duplex communication channel. We work on the tracking algorithm to determine the pupil position continuously as the eye moves around to re-target an infra-red laser to power the implant and send forward data such as a world view encoded images captured with an external camera. We use Machine Learning techniques implemented on FPGA-based hardware to accelerate the computation speed and yield better power performances.

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Model-based Recommendations for Optimal Surgical Placement of Epiretinal Implants

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Purpose: A major limitation of current electronic retinal prostheses is that in addition to stimulating the intended remaining retinal ganglion cells, they also stimulate passing axon fibers, producing perceptual 'streaks'1,2 that limit the quality of the generated visual experience3. Recent evidence suggests a dependence between the retinal location of the stimulated electrode and the shape of the generated visual percept4. Here we examine whether incorporating this knowledge into the surgical placement of epiretinal implants has the potential to improve visual outcomes.

Methods/Results: Using a psychophysically validated computational model4,5, we explored the space of possible implant configurations to make recommendations for optimal intraocular positioning of the electrode array. Currently, surgeons are instructed to place the array parafoveally roughly diagonal at 45° clockwise to the horizontal meridian6. We demonstrate that the optimal implant location, as inferred from a population of virtual patients, is ~2000μm temporal to the fovea, centered over the horizontal meridian, and oriented at ~10° counterclockwise to the horizontal (Fig. 1). Adjusting implant placement has the potential to reduce the spatial extent of axonal activation in existing retinal implant users by up to ~55% (Fig. 2). Importantly, this configuration is surgically feasible7, and is relatively consistent across individuals.

Conclusion: The visual outcome of epiretinal implant surgery might be substantially improved by guiding the intraocular positioning of the electrode array using a patient-specific computational model of the spatial layout of the optic fiber layer. This study is a first step towards the use of computer simulations in the patient-specific planning of retinal implant surgery.
Competing interests: All authors are collaborators with Second Sight Medical Products, Inc. (SSMP). SSMP had no role in study design, data analysis, decision to publish, or preparation of the abstract.

Biography: Michael Beyeler earned a PhD in Computer Science at UC Irvine as well as a BS in Electrical Engineering and a MS in Biomedical Engineering at ETH Zurich, Switzerland. As a postdoctoral fellow in Neuroengineering & Data Science at the University of Washington, he developed computational models of bionic vision, which led to a NIH K99/R00 Pathway to Independence Award. In January 2020, he will join the faculty at UC Santa Barbara to form the Bionic Vision Lab.

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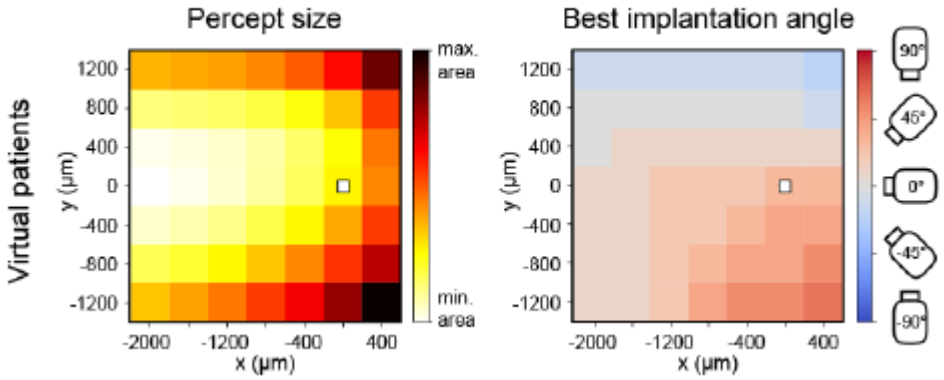

Figure 1: Simulated phosphene size for different implant configurations in a population of virtual patients. Left: Minimal phosphene size achieved by optimal device rotation with the array centered at each location. Right: Device orientation used to achieve minimal phosphene size in the left column. Small squares: fovea.

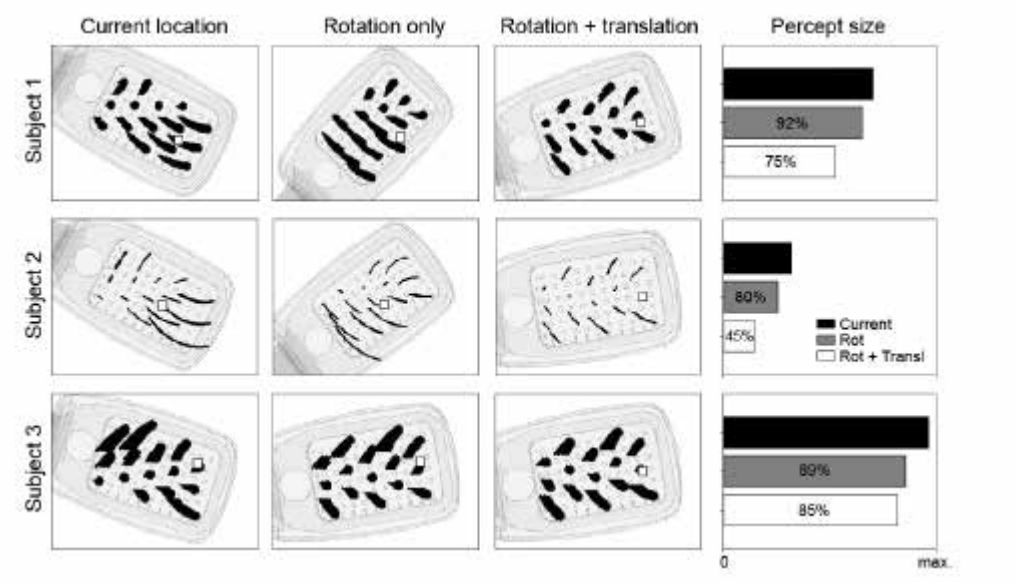

Figure 2: Model predictions of percept shape for three Argus II subjects. Leftmost: Predictions for the actual implant configurations. Second column: Same location, but device orientation is adjusted to minimize the spatial extent of axonal activation. Third column: Both device location and orientation are optimized. Rightmost: Mean phosphene size. Small squares: fovea.

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Retinotopic to Spatiotopic Mapping in Blind Patient Implanted with Visual Cortical Neurostimulator

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Purpose: Treating blindness due to diseases that severely compromise the optic nerve will require stimulation at locations in the visual pathway that bypass the eye and the optic nerve. In sighted individuals, due to eye movements, the brain continuously maps visual information acquired at retina-based coordinates to spatial locations in world-based coordinates. Correspondingly, electrical stimulation of visual cortex in blind patients should convey information to the brain that is mapped to the correct spatial location in the world. The purpose of this study was to verify that electrical stimulation of the visual cortex of a blind patient is correctly mapped based on eye position.

Methods: Electrical stimulation of the visual cortex of a blind subject with bare light perception secondary to Vogt-Koyanagi-Harada syndrome was achieved using the RNS neurostimulator (NeuroPace, Mountain View, CA). Two parallel strips of four electrodes each were implanted over the right medial occipital lobe.

The subject reported the location of the percept from electrical stimulation of a single electrode using a trackable handheld marker. Eye positions were recorded with a timestamp synchronized to the time of stimulation.

Results: The perceived location, resulting from electrical stimulation of the visual cortex, shifted based on the eye position at the time of the stimulation. We were able to remap the measured responses based on measured eye position in order to localize the retinotopic locations associated with each electrode.

Conclusions: Artificial vision generated by electrical stimulation at the occipital lobe creates a percept that is mapped to world-based coordinates based on eye and head positions. The brain of a blind individual has the necessary signals to accurately map visual information necessary to utilize eye movements for visual scanning.

Biography: Dr. Caspi is the chairman of the Department of Electrical and Electronics Engineering at Jerusalem College of Technology and a consultant 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 retinal prostheses, eye movements and sensor integration for visual prosthesis devices.

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Recessed Electrodes Enable Subretinal Prosthesis with Cellular-Scale Pixels

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Purpose: High-resolution retinal prostheses require small, densely packed pixels for localized neural stimulation, but limited penetration depth of the electric field formed by a planar electrode array constrains such miniaturization. We present a novel honeycomb configuration of an electrode array with vertically separated active and return electrodes designed to leverage migration of retinal cells into the pixel cavities. In this configuration, electric field is aligned vertically to match the orientation of bipolar cells in the retina, which should significantly reduce the stimulation threshold and decouple the penetration depth of electric field from the pixel size.

Methods: To study retinal integration with the honeycomb implants, inactive arrays were fabricated in silicon with 25 μm tall walls separating cavities of 40, 30 and 20 μm in width. Devices were implanted beneath the degenerate rat retina (RCS) for 6 weeks, and then observed using OCT, immunohistochemistry, and histology. Stimulation thresholds with such arrays were assessed using finite element calculations of electric field and a model of network-mediated retinal stimulation validated by previously recorded experimental data. Polymer walls of 30 μm in height were also fabricated with two-photon lithography on top of the active photovoltaic arrays with 55 μm pitch.

Results: More than half of the inner retinal neurons migrate into the honeycomb cavities of all widths. The layered structure of the retina is preserved with both inactive and active arrays. Glial response with honeycomb arrays is similar to that observed with planar implants, where elicited VEP under prolonged retinal stimulation indicates no adverse effect on the retinal responsivity. Calculated stimulation threshold current density with honeycombs does not significantly change with pixel size, unlike the quadratic increase with the reduced pixel size of the flat arrays. As a result, calculated threshold with 20 μm honeycomb pixels is 34 times lower than that of planar pixels of the same size. Compartmentalization of the inner retinal neurons into cavities should preserve 100% spatial contrast for all pixel sizes within the SIROF charge injection limit (<3 mC/cm2), while allowing activation of up to 100% of the cells in the inner nuclear layer in front of the implant.

Conclusions: The honeycomb-shaped subretinal prosthesis decouples the penetration depth of electric field in tissue (set by the height of the walls) from the pixel width, and thereby overcomes the limitations of decreasing pixel size. This approach may enable scaling the pixel size to cellular dimensions to provide visual acuity better than 20/100. Coupled with the structural simplicity of the photovoltaic retinal prosthesis, this approach may enable highly functional restoration of central vision in patients with advanced age-related macular degeneration.

Biography: Zhijie (Charles) Chen is a Ph.D. candidate at Stanford University. He conducts research in photovoltaic retinal prosthesis in Hansen Experimental Physics Laboratory, advised by Dr. Daniel Palanker. He is interested in brain-machine interfaces and neuro-electrical engineering. His past research topics include wireless communications and signal processing. He received the degrees of B.Eng. and of M.S. from Tsinghua University in 2017 and from Stanford University in 2019, respectively, both in electrical engineering, with an undergraduate minor in economics. Charles was a Physics Olympiad competitor, and in math he trusts.

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Analyzing Prosthetic Visual Performance Using Signal Detection Theory (SDT)

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Purpose: When psychophysical measures are obtained from stimuli with a latent variable such as item difficulty, conjoint methods such as Rasch analysis are required to estimate both person and item measures. Previously (Adeyemo, ARVO #4688, 2017) we applied this approach to data from individuals with ultra-low vision (ULV) performing real-world activities with 2-, 3-, or 4-alternative force choice (AFC) judgments. However, since Rasch analysis ignores correct performance by chance, item measures from mixed m-AFC instruments should be questioned. A different approach, based on SDT and yielding person and item measures in d' units, has recently been introduced. Here we compare the two approaches.

Methods: Performance data from 17 activities, at 3 difficulty levels, each performed twice by 25 individuals with native ULV and 4 Argus II and 6 Brainport users, were submitted to both analyses. Confidence intervals (CIs) and fit statistics were obtained in Winsteps© for Rasch analysis, whereas the SDT-based analysis does not currently yield CIs for person measures with unequal probability test items.

Results: Both person (left panel) and item (right panel) measures show excellent (r^2>0.995) correlation between the two methods. However, under SDT-based item measures for 2-, 3-, and 4-AFC activities are shifted relative to Rasch item measures, as would be expected: In Rasch analysis 2-AFC activities are fitted as relatively easier, and 4-AFC activities as harder, than 3-AFC activities due to different chance correct rates, whereas SDT-based items measures are estimated correctly. This explains the 3 parallel linear clusters. In the conversion from logit intervals (Rasch) to d' intervals (SDT), item CIs scale roughly proportionally with the item intervals.

Conclusions: Our results demonstrate that the SDT-based analytic approach can successfully handle data from mixed m-AFC instruments, and otherwise produces estimates that closely correspond to those obtained from Rasch analysis. It is thus a powerful tool for conjoint analysis of psychophysical data.

Biography: Gislin Dagnelie, Ph.D., is an Associate Professor of Ophthalmology in the Johns Hopkins University School of Medicine and the associate director 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 is the Center Principal Investigator for clinical trials of the Second Sight Argus™ II retinal implant (2007-present) and is leading several follow-up engineering studies to make Argus II use more productive in patients' daily lives. In addition, he studies signals in the retina of retinal prosthesis patients, is involved in the development of phosphene mapping and psychophysical assessment strategies for the Chicago-based intracortical prosthesis project, and is leading the development of assessment and rehabilitation methods for visual prosthesis wearers and other individuals with ultra-low vision.

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Fabrication and Analysis of Iridium Oxide based Microbump and Mushroom Geometry Electrode Designs

Angela Elias, Michelle Brusatori, Greg Auner

Purpose: The neural-device interface is arguably the most important topic to consider when designing a device. The biggest barrier to cross is the foreign body response and unintended cross talk between stimulation points. Examples of foreign body response affecting device functionality are inflammation and scar tissue formation. In both cases, the signal from the device is weakened - perhaps to the point of complete inhibition. Further the geometric design of the electrode can affect the stimulating signal. Previous research has shown that as the device gets smaller, the foreign body response is essentially mitigated. Furthermore, exotic electrode designs such as a mushroom geometry compared to planar electrodes may localize stimulation to the area of contact. In our lab, we have fabricated activated iridium microbump electrode arrays. The microbump geometry had diameters of 4-5 μm and heights of 1-2 μm. This geometry will be compared to a novel activated iridium mushroom shaped electrode design.

Method: The iridium oxide microbumps were fabricated using Eximer laser micromachining. In contrast, activated iridium mushroom geometry electrodes are fabricated by electrodeposition. Electrode characterization was performed by Raman spectroscopy, X-ray photoelectron spectroscopy (XPS), AFM, and electrical impedance characterization. Simulations using COMSOL simulation software was used to model the electrode designs and compared to the experimental results.

Conclusions: Characterization of our electrode array using simulation, compositional, and electrical measurements demonstrate biocompatibility features and increased electric field confinement.

Biography: Angela Elias started at Wayne State University as a pre-optometry major which led her to pursue a B.S. in Biochemistry and Chemical Biology as well as a B.S. in Psychology. This is also where she entered the research world. Angela worked in a computational physical chemistry lab on analysis of a putative checking site in a specific DNA polymerase. During that time, she also worked in the optometry field for a few years. Working in both fields made her realize she had a greater passion for research than she knew. Flash forward a few years, and she is now a Ph.D. candidate in Biomedical Engineering working on a design, fabrication, and analysis of an electrode array for retinal implants.

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A Patient-Specific Computational Framework for the Argus II Implant: Using Multiple Imaging Modalities to Account for Disease Progression and Device Placement

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Purpose: Electrical stimulation of retinal tissue via the Argus II implant induces visual percepts for profoundly blind subjects with retinal degenerative diseases. Percepts are consistent for single electrodes trial to trial but vary across subjects and electrodes (Luo 2016). It is hypothesized that computational models can predict variation caused by device placement, fibrous tissue formation near the electrode array, and disease progression. The purpose of this project was to develop a methodology to incorporate multi-modal imaging data into a patient-specific eye model with accurate anatomy and implant placement.

Methods: Ultrasound and optical coherence tomography (OCT) images were obtained at the Kellogg Eye Center from an Argus II patient. A-scan ultrasound (n=5) measured axial length and anterior chamber depth. L3 longitudinal (n=5) and 12E transverse (n=5) B-scan ultrasound measured horizontal/vertical vitreous diameter, and position of the extraocular electronics case. These parameters were used to reconstruct the patient's eye shape and define the current return (the top part of the electronics case) in a COMSOL model. OCT images were taken over the implant center, spanning 30° x 25° of the visual field. Mimics (Materialise, NV, Lueven, Belgium) was used to segment the patient's retina and create a finite element mesh, which captured retinal thickness and fibrotic tissue response. Before segmentation, images were corrected for posterior shape distortion (Kuo 2013). The mesh was registered with the COMSOL model using the optic nerve as a control point. The Argus II microelectrode array was also segmented from OCT images. A global distance minimization algorithm was used to register an accurately detailed microelectrode array with the segmented shape.

Results: The model accounts for overall eye shape, current return position, microelectrode array position, retinal thickness, and fibrotic response. Each factor was captured for a specific patient using two co-registered imaging modalities. The patient-specific retinal mesh and whole eye model are shown below. In COMSOL, electrical conductivities were assigned and finite element electric field solutions were generated by applying current in the clinically allowable range (0-233 μA) to single electrodes.

Conclusion: Future work will validate this modelling framework with patient threshold maps obtained clinically. Once validated, the model can optimize device performance for individual patients.

Biography: Kathleen Finn completed her Bachelor of Science (B.S.) in Biomedical Engineering at Hope College in Holland, Michigan. She is now pursuing a Ph.D. at the University of Michigan, conducting research in Dr. James Weiland's BioElectronic Vision Lab. Her focus is the development of computational models to study and optimize retinal prostheses.

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Studying The Effect of Order And Duration Ratio of Pulse Polarities on Perception Shapes With Argus II Retinal Prosthesis

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Purpose: Retinal prosthetic implants have helped improve vision in blind patients with retinitis pigmentosa (RP) and age-related macular degeneration (AMD), two of the common retinal diseases that lead to loss of photoreceptors and eventual blindness. Although patients with retinal implants have reported improvement in light perception and performing visual tasks, their ability to perceive shapes and letters is currently limited due to the low precision of retinal activation. A previous in vitro mouse retina study in our lab (Chang et al. 2018) used calcium imaging to measure the spatial activation of RGCs in response to electrical stimulation. Based on this study, we hypothesize that symmetric anodic-first pulses avoid axonal stimulation and create focal RGC activation. We also showed that asymmetric anodic-first stimulation decreases RGC activation thresholds but it can only create focal responses in a narrow range of amplitudes.

Methods: We are currently performing human subjects testing to further examine the effect of symmetric and asymmetric anodic-first pulses on perception shape characteristics including area and elongation. In two Argus II retinal prosthesis subjects, we measured responses to asymmetric anodic first (AAF), symmetric cathodic first (CF), and symmetric anodic first (AF) stimulation, by having the subjects draw the shape of the phosphene on a touch screen, then measuring the area of the drawing and the elongation (ratio of major axis to minor axis of an ellipse fit to the shape).

Results: Our results on the first subject show a significant increase in the percept area using AAF stimulation compared to CF stimulation, with pulse durations of 0.1 and 0.2 ms. The second subject shows significantly less elongated percepts using AF compared to CF stimulation with 0.1 ms pulse duration. We observed an increase in phosphene size with increasing the duration ratio (ratio of the anodic phase duration to the cathodic phase duration) of the AAF pulse, regardless of the total delivered charge and pulse duration. These observations are consistent with our previous in vitro findings. Phosphene shape comparison for the third subject did not show any significance, possibly due to this subject's high rate of spontaneous activity and desensitization to stimulation.

Biography: Dorsa Haji Ghaffari is a third year Ph.D. student in biomedical engineering at University of Michigan. She has completed a master's program in biomedical engineering at University of Michigan, and a bachelor's in biomedical engineering at Science and Research Branch of Islamic Azad University in Tehran, Iran. Her research is focused on improving the resolution and efficacy of electrical stimulation in retinal implants.

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Electrical Recording and Stimulation of Rgcs in the Macaque Raphe at Cellular Resolution

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Objective: For epiretinal implants, it is desirable to focus on areas of the retina where unwanted axon activation and consequent arc-like phosphenes are least likely. One such region is the raphe, representing 0-20° eccentricity on the temporal horizontal meridian. However, to faithfully reproduce normal patterns of retinal ganglion cell (RGC) activity, an implant must also be able to efficiently record and stimulate individual cells. Here, electrical recording and stimulation at cellular resolution in the raphe are explored.

Methods: Preparations of isolated macaque retina were stimulated and recorded on the RGC side using a custom 519-electrode array (30μm pitch, 8-15μm diameter electrodes, 0.43mm 2 area). 15 recordings from regions 2-3 mm (10-15°) from the fovea along the temporal horizontal meridian were obtained. Light responses of RGCs were analyzed by reverse correlation with white noise visual stimuli. The electrical image for each RGC (average spatiotemporal pattern of electrical activity on the array associated with a spike, EI) was also examined. Following visual stimulation, RGCs were electrically stimulated using triphasic charge balanced current pulses (0.1 - 4 μA). Automated and manual spike sorting were performed to separate evoked spikes from electrical artifact.

Results: Analysis of visual responses indicated that the five major RGC types in the macaque retina were recorded: ON parasol, OFF parasol, ON midget, OFF midget, and small bistratified.For parasol cells, receptive field mosaics were sometimes nearly complete, indicating efficient recording. For the other cell types, recordings were less efficient. In one preparation, ~200 RGCs of the five dominant types were recorded. EIs of recorded RGCs sometimes exhibited axons traveling in opposite directions away from the recording site, consistent with the unique anatomical organization of axons in the raphe. The amplitude of recorded spikes was lower than that of similar recordings in the peripheral retina. Analysis of electrical stimulation revealed that in some cases, activation of single RGCs without activating neighboring cells of the same type was possible, at stimulation current levels that did not activate axon bundles.

Conclusions: Efficient recording and stimulation of the five major RGC types at high resolution is possible in the raphe area of the macaque retina. These results support the viability of targeting the raphe with a cellular-resolution epiretinal implant.

Biography: Alex Gogliettino is a third year Neurosciences PhD student at Stanford University. Previously, he completed a BS in Neuroscience at Bates College. Alex is currently working on retinal electrophysiology in Professor E.J. Chichilnisky's lab.

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Effect of a Post-Vitrectomy Injection of Sodium Iodate on Retinal Degeneration in Dogs

Purpose: In comparison with normal retina, degenerated retina shows abnormal histological and physiological features. Thus, understanding of retinal degeneration (RD) network through animal model is a prerequisite for the development of retinal prosthesis for the blind. Although RD mouse is a well-established genetic model, due to huge gap in species and eye size between human and mouse, it is necessary to develop large size animal model close to human. Since the benefit of post-vitrectomy injection of drug for RD was reported in rabbit, here we report a new canine model of drug-induced RD with post-vitrectomy injection of sodium iodate (SI).

Methods: SI (1.2 mg) was injected at 2 weeks after vitrectomy in the right eyeball of canines (n=6). To observe histological changes with SI injection, we performed H&E staining and immunohistochemistry (IHC) after 1 (n=1), 3 (n=2) and 6 (n=2) months of injection. Also, we recorded the spiking activity of retinal ganglion cells (RGCs) in response to light (full field flash) and electrical stimulation in 4 different retinal regions which are Tapetum Lucidum-Nasal (LN), Lucidum-Temporal (LT), Nigrum-Nasal (NN) and Nigrum-Temporal (NT) with in-vitro multielectrode array (MEA) recording at 6 month after SI injection.

Results: In H&E and IHC study, PNA and rhodopsin signals decreased rapidly after 3 months but not disappeared completely, although PKCμNeuN and GFAP signals rarely changed. In MEA study, we observed debatable finding in SI-injected retina: In comparison with typical ON, OFF and ON-OFF responses in normal retina, LN and NT regions showed a loss of light response. But LT and NN regions preserve light response. The electrical responses of RGCs were found in both SI-injected and normal retinal patches.

Conclusion: In histology, 1.2 mg of SI induced the localized RD only in outer not in inner retina of canine model. However, in MEA recording, LN and NT regions lost light evoked response, which was opposite with the response of LT and NN regions. First, SI dose optimization is needed to establish solid outer RD model in dogs which might be applied to a preclinical study for developing the retinal prosthesis.

Biography: Yong Sook Goo is Professor of Physiology in the School of Medicine at the Chungbuk National University at Cheongju, South Korea. Her education includes a MD (1988) from Seoul National University and a PhD in Physiology (1993) from Seoul National University, Seoul, Korea and she completed post-doctoral training (1996-1998) in Department of Physiology, Tulane University Medical School. Dr. Goo has directed several projects funded by the KOSEF, KRF, and Ministry of Health and Welfare on retinal network study for retinal prosthesis since 2001. Her major research interest is on the retinal network analysis.

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Education
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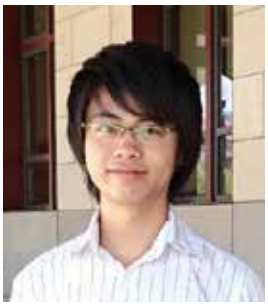


Elton Ho, B.Sc.
Stanford University
Stanford, California

Prosthetic Vision with Grating Acuity under 50 Um

Ho, Elton1,2, Lei, Xin3, Flores, Thomas4, Lorach, Henri2, Huang, Tiffany W.3, Kamins, Theodore3, Galambos, Ludwig2, Mathieson, Keith5, Palanker, Daniel2, 6 1. Department of Physics, Stanford University, Stanford, CA, United States. 2. Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, United States.3. Department of Electrical Engineering, Stanford University, Stanford, CA, United States. 4. Department of Applied Physics, Stanford University, Stanford, CA, United States. 5. Institute of Photonics, University of Strathclyde, Glasgow, United Kingdom. 6. Department of Ophthalmology, Stanford University, Stanford, CA, United States.

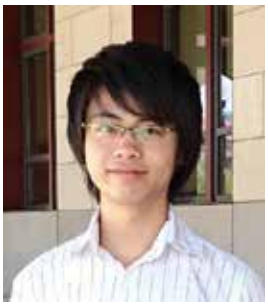
Purpose: In clinical trials of the current retinal implants, prosthetic visual acuity does not exceed 20/460. However, to provide meaningful restoration of central vision in patients blinded by age-related macular degeneration (AMD), prosthetic acuity should, ideally, exceed 20/200, necessitating a pixel pitch of about 50 μm or lower. With such small pixels, stimulation thresholds are high due to limited penetration of electric field into tissue. Here, we address this challenge with our latest photovoltaic arrays and evaluate their performance in-vivo.

Methods: We fabricated photovoltaic arrays with 55 and 40 μm pixels (a) in flat geometry, and (b) with active electrodes on 10 μm tall pillars. Pillars were electroplated with gold on top of the pixels, and had hemispherical caps coated with sputtered iridium oxide film (SIROF). The arrays were implanted subretinally into rats with degenerate retina. Stimulation thresholds (irradiance and duration) and grating acuity were evaluated using measurements of the visually evoked potentials (VEP).

Results: Irradiance thresholds with flat pixels ranged between 1 and 2 mW/mm2, and duration thresholds ranged between 0.3 and 0.8 ms. With pillar electrodes, the irradiance threshold was nearly halved, and duration threshold reduced by more than 3-fold. With 55 μm pixels, we measured grating acuity of 48±11 μm, which matches the linear pixel pitch of the hexagonal array. This geometrically corresponds to a visual acuity of 20/192 in a human eye, exceeding the threshold of legal blindness in the US (20/200). With 40 μm pixels, VEP was too low for reliable measurements of the grating acuity, even with pillar electrodes.

Conclusions: In rats with retinal degeneration, hexagonal arrays with 55 μm pixels provide grating acuity matching the row spacing of 48 μm, which in a human eye geometrically corresponds to visual acuity exceeding the threshold of legal blindness (20/200). If successful in clinical testing, such arrays could provide highly functional prosthetic vision, even for patients with the loss of only central vision, as in AMD. Scaling the pixel size further down is difficult even with pillar electrodes since stimulation thresholds approach the ocular safety limit and the cortical signal becomes too weak for electrophysiological measurements.

Biography: Elton Ho is a sixth-year Physics PhD student at 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.



Elton Ho, B.Sc.
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Perceptual Performance on Complex Visual Tasks Using Simulated Prosthetic Vision with Augmented-Reality Glasses

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Purpose: Photovoltaic subretinal prosthesis is designed for restoration of central vision in patients with atrophic age-related macular degeneration (AMD). Therefore, it is vital to understand the utility of such devices for complex visual tasks, such as reading and face recognition, within the expected limitations on resolution, dynamic range and the visual field size in prosthetic vision. Here, we studied the performance of healthy subjects on various psychophysical tasks with simulated prosthetic vision using augmented-reality (AR) glasses.

Methods: We simulated prosthetic vision using a pair of AR glasses (ODG R6) with blocked central vision. An integrated camera on the goggles captures a real-time video that is processed through a custom Android app. The software adjusts the video quality according to three user-defined parameters: equivalent pixel size of an implant (20-100 μm), field of view (7-12 degree), and number of contrast levels (2-256). The processed video is then streamed on a screen in the goggles. Test images were displayed on a monitor placed 30" away from a chinrest. Nineteen healthy participants were recruited to complete the visual tasks including vision charts, face recognition, and sentence reading.

Results: Both with Landolt-C and Snellen acuity charts, visual acuity was better than the pixel-sampling limit by 0.1 logMAR. In a face recognition task (4-way forced choice), participants could identify 5°x5° faces at >75% accuracy, even with 100 μm pixels and only 2 levels of contrast. With 60 μm pixels and 8 levels of grey, the accuracy exceeded 97%. For sentence reading, in addition to limitations by the pixel size, restricted field of view (from 12 to 7 degrees) reduced the maximum reading speed from 165 to 130 words per minute, especially for contextually and lexically simple sentences.

Conclusions: Healthy subjects with central "prosthetic vision" simulated by reducing the spatial resolution, dynamic range and visual field on AR glasses performed close to the sampling limit on the resolution tasks, with all levels of contrast. Even with 100 μm pixels and binary contrast, success in recognition of 5°-wide faces was about 75%, and it increased to nearly 100% with 60 μm pixels and 8 levels of grey. These results indicate feasibility of the reading and face recognition with prosthetic central vision even with 100μm pixels, and performance improves further with smaller pixels.

Biography: Elton Ho is a sixth-year Physics PhD student at 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.

Saad Idrees, M.Sc.
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Tuebingen, Germany

Saccadic Suppression by Way of Retinal-Circuit Image Processing

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Purpose: Self-movement, in particular eye movements during active visual exploration, such as saccades, are the dominant cause of image flow across the retina. When designing visual prosthetic devices, it is important to consider the effects of such dominant viewing statistics. Here, we characterized the effect of saccade-like image shifts on visual processing in healthy retina.

Methods: We used ex-vivo retinal electrophysiology and recorded from more than 1,000 retina ganglion cells (RGC's) in isolated mouse and pig retinae. We mimicked saccade-induced retinal image shifts by translating a background image. We then tested the effects of those mimicked saccades on brief test stimuli presented at different delays. We varied background image statistics and test stimulus luminance, and we also investigated center-surround interactions and amacrine cell contributions to retinal saccadic suppression.

Results: Retinal responses to test stimuli, when presented in the context of saccades, were strongly suppressed in comparison to responses to the same stimuli presented in isolation. Such saccade-related retinal suppression occurred robustly across many different RGC cell types. Suppression properties critically depended on the delay between saccade and test stimulus, as well as on the statistical properties of the background scene present during the saccades. In ON RGCs, the suppression lasted for up to 1s, whereas OFF RGCs tended to recover much faster. The suppression did not critically depend on particular saccade-like profile speeds but was a result of general stimulus-stimulus interaction effects triggered by image displacements. A component of this suppression originated from wide-field amacrine cell mediating inhibition. Another component originated from the ganglion cell's receptive field center.

Conclusion: Saccadic suppression does occur robustly across many different RGC cell types and is a result of specific spatio-temporal retinal-circuit image processing. Such retinal processing can motivate the development of specific image processing algorithms for an active vision based visual prosthesis device.

Funding: This work was supported by funds of the Deutsche Forschungsgemeinschaft (DFG) to the Werner Reichardt Center for Integrative Neuroscience (EXC 307) and to T.A.M. (MU3792/3-1). T.A.M. received support from the Tistou and Charlotte Kerstan Foundation. T.A.M. and Z.M.H. were also supported by an intra-mural funding program (Projekt 2013-05) of the Werner Reichardt Centre for Integrative Neuroscience. F.F. was supported through a Swiss

Biography: Saad Idrees is currently doing his Ph.D. with Thomas Münch at the University of Tuebingen in Germany, where he studies how retina processes information under dynamic conditions of active vision. He did his bachelor's in engineering sciences from Pakistan and later on did his master's in biomedical engineering from Imperial College London where he worked on developing computer vision applications aimed to aid blind people undertake everyday tasks. His interests lie in bridging the gap between biological and computer vision in the context of visual prosthesis.

Nadav Ivan, Ph.D.
Bar-Ilan University
Ramat-Gan, Israel

High Resolution Visual Cortex Retinotopy for Studying Prosthetic and Natural Vision

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Purpose: To understand cortical interactions between prosthetic and natural vision, it is important to map cortical responses to prosthetic and natural stimuli at high resolution.

Method: Toward this end, we used voltage-sensitive dye imaging (VSDI) to record the visual cortex responses in rats. For stimulation, we used a custom-built projection system consisting of a DMD projector with real-time retinal imaging to enable stimulus positioning on the retina. Using a green LED (530 nm) and a NIR diode laser (915nm) we elicited retinal response either naturally, or via photovoltaic subretinal implant, respectively.

For generating high-resolution retinotopic mapping in visual cortex, we first stimulated the natural retina with 8 pulsed stimuli, with the center to center distance of 270 μm (which corresponds to 4.6 degrees) at 1 Hz repetition rate. Resulting retinotopic mapping revealed that nasal retinal stimuli elicited responses at the medial-posterior area of V1, whereas temporal retinal stimuli elicited responses at the lateral-anterior area of V1, in agreement with previous reports. We then stimulated rats with subretinal photovoltaic implants with pixel sizes of 140 and 280 μm using full-field NIR flashes. The resulting VSDI responses had comparable dynamics to natural activation.

Similarly to experiments with the natural retina, we used patterned prosthetic stimuli to generate prosthetic retinotopic mapping of the visual cortex. The resulting maps were comparable to those obtained by the natural vision, with the implant region corresponding to a highly localized activation area in the cortex.

The presented method can serve as an important tool to further explore the cortical responses to prosthetic retinal activation, and for studying the combined prosthetic and natural responses, which are important for restoration of sight in age-related macular degeneration.

Biography: Doctor Nadav Ivzan received his bachelor's degree in biomedical engineering from Boston University (class of 2008) where he studied visual properties of Horseshoe crabs ommatidial units and won the best senior project award for his work. Nadav continued for doctoral degree studies at the University of Southern California under the guidance of Professor Norberto Grzywacz to perform retinal electrophysiology and develop computational models that predict ganglion cell responses to natural stimuli. After receiving his Doctoral degree (2014) Nadav worked for a startup company developing a hippocampal prosthesis based on Professor Ted Berger's vision. In 2016 Doctor Ivzan decided to go back to academia and took a postdoctoral position at Bar-Ilan University under the guidance of Professor Yossi Mandel finely activating subretinal photovoltaic implants and recording the responses using Voltage Sensitive Dye Imaging (VSDI) technique.

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

The Effect of a Distance Filtering Camera on Orientation and Size Discrimination Tasks in Argus II Users

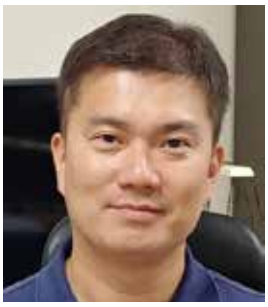
Purpose: The Argus II retinal prosthesis system was developed for people who are blind from end stage retinal degenerations. Argus II users have reported improvements in their functional vision ranging from improved light perception to reading large letters. However, its limited spatial resolution increases cognitive load to extract useful information in the presence of multiple or conflicting stimuli, e.g. an open cabinet in the kitchen or reaching for a cup on a table with a patterned tablecloth. The current study investigated the use of a distance filtering system, which is a stereo based set up with two cameras mounted on the temples of glasses, on the performance of an orientation and size discrimination task by Argus II users.

Methods: Three experienced Argus II users participated in the study. The task was to determine the location(s) of 1, 2 or 3 objects (66, 44 and 22 inches long), covered with a random dot pattern, that were suspended from the ceiling at three possible locations: center, 45 degrees to the right and 45 degrees to the left at 1m from the subject. Subjects were asked to scan with their head and to report if they located the target object(s). In cases of double and triple objects, they were asked to report the size of the objects. The camera's input was monitored during the experiment. The distance filter range was set for a maximum distance of 1m so that all objects beyond the set distance were digitally redacted.

Results: Mean accuracy and response times were compared between visible and distance filter cameras using d prime analysis. Subjects had significantly lower d-prime values with the distance filter ($p<0.05$), showing better performance. Response times with the distance filter were less than half those with the visible camera. A paired sample t-test showed that size discrimination was significantly more accurate with the distance filter ($M=87.8\pm 97.1$) compared to visible camera ($M = 38.9\pm 27.98$) ($t(3) = -7.54$; $p = 0.0048$).

Discussion: In our experiments, we found that the 3 experienced Argus II users benefited significantly when the image was decluttered digitally by using a distance filtering camera. All 3 subjects had higher accuracy and speed for an orientation task using hanging objects which would be difficult to detect using their habitual white cane that is more useful for objects close to ground level. They were also able to discriminate between different object sizes more accurately with the distance filter, which could be an advantage for real world situations where objects in the range could only be differentiated based on sizes.

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.



Seong-Woo Kim, MD
Department of Ophthalmology
Korea University College of Medicine
Seoul, Korea

The Effects of Intravitreal Sodium Iodate Injection on Retinal Degeneration Following Vitrectomy in Canine

Seong-Woo Kim, MD1*, PhD, So Min Ahn, MD1; Yong-Jin Kim3; Yongsook Goo, MD, PhD2* 1Department of Ophthalmology, Korea University College of Medicine,
2Department of Physiology, Chungbuk National University School of Medicine, Cheongju, Korea 3Medical Device Development Center, Osong Medical Innovation Foundation, Cheongju, Korea

Purpose: We developed and characterized a canine model of outer retinal degeneration induced by sodium iodate (SI) intravitreal injection after vitrectomy.

Methods: In the dose-dependence study, we repeatedly injected SI intravitreally in the right eyes of three female mixed breed dogs to develop outer retinal degeneration two weeks after vitrectomy. In the second efficacy study, based on the dose-dependence study, 1.2 mg SI/0.05 ml was injected into the right eye of five canines two weeks after vitrectomy. Additionally, 1.0 mg SI/0.05 ml was injected into the right eye of two canines two weeks after vitrectomy. Spectral-domain optical coherence tomography (OCT), infrared fundus photography (IR-FP), and electroretinography (ERG), and histological examinations with hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) were performed at baseline and after intravitreal injection.

Results: In the dose-dependence study, in first dog, after two times of 0.5 mg SI injection followed by 1.0 mg SI injection, severe retinal atrophy of the whole retina was induced in the OCT. In the second dog, after two times of 0.8 mg SI injection, severe retinal atrophy of the whole retina was induced in the OCT. In the third dog, after single 1.2mg SI injection, outer retinal degeneration was induced. In the second efficacy study, all 5 eyes showed diffuse outer retinal degeneration in OCT and loss of both cone and rod response in ERG. Histological examination also showed the loss of outer nuclear layer and photoreceptor layer.

Conclusions: Intravitreally injected SI (1.0 to 1.2 mg) in a vitrectomized canine model could induce outer retinal degeneration effectively, and the degree of retinal degeneration could be evaluated through in-vivo ophthalmic examination.

Biography: Professor Seong-Woo Kim is a retinal specialist and has worked as a faculty member of Department of Ophthalmology, College of Medicine, Korea University since 2008. His research topic is Retinal Prosthesis and now he is leading a research group as a principal investigator. He received the Korean government research fund (3.5 million dollars for 5 years) for retinal prosthesis development at 2017. Prof Kim is developing retinal degeneration model in large size animal and implanting the chip inside animal eye as well as managing the research group.

Denis Kuleshov
ANO "Laboratory "Sensor-Tech" and the
Deaf-Blind Support Foundation "Con-nection"
Moscow, Russia

Andrey M. Demchinsky, Ph.D.
Laboratory "Sensor-Tech"
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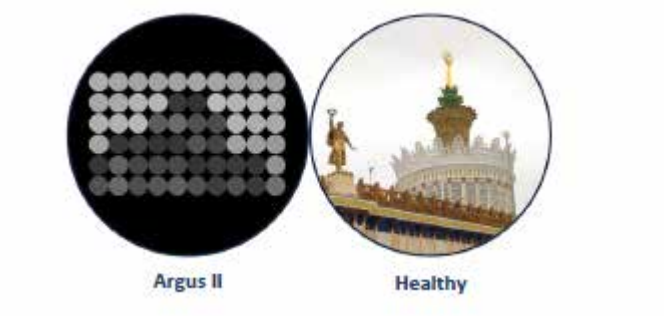
Dmitry Polikanov, Ph.D.
Deaf-Blind Support Foundation "Con-nection"
Moscow, Russia

Ophthalmic VR-Simulator in Rehabilitation of Patients with Bionic Vision

Vision impairments and blindness are global challenges. According to WHO, nowadays there are about 39 million blind people in the world. Considerable attention is paid to the methods of treatment and prevention of eye pathologies. Rehabilitation of patients is equally important, including those patients who have lost vision, and the issues of their social adaptation. Eye diseases can be reversible and irreversible. Nowadays to some of the irreversible diseases there is treatment, to some – still not and to some they start to invent new treatment, such as retinal prostheses systems for retinitis pigmentosa.

In 2017 ANO «Laboratory «Sensor-Tech» took part in implementing first «Argus II» retinal implant surgeries in Russia and presently carries out rehabilitation activities with the patients by place of their residence. To provide a rehab specialist with a better understanding of how the patients see objects and surrounding space around them, there was developed an Ophthalmic VR-Simulator to imitate eye diseases and bionic vision which works in the similar to «Argus II» way: the image from the camera gets averaged to 60 pixels in black-and-white format, with a function to change the contrast level, blurring and size of phosphenes, turn off particular electrodes, change the size of each electrode and the frame repetition rate. The software of the «Argus II» producing company allows to see the simulation with the eyes of the RPS user, however, a rehabilitation specialist does not have an opportunity to use it for self-studying the forms of objects from different sides to subsequently describe them to the patient and indicate the significant elements that the patient should pay attention to. The developed Ophthalmic VR-Simulator provides this opportunity.

The Ophthalmic VR-Simulator could also be used to evaluate the surrounding space by place of residence of the patients in order to understand what changes are needed to maximize the effectiveness of RPS: the rehab specialist studies a house (an apartment) or adjacent surroundings to home and decides when contrast accents (markers to pay attention to) are needed for the patient to be able to orient him- or herself more easily.



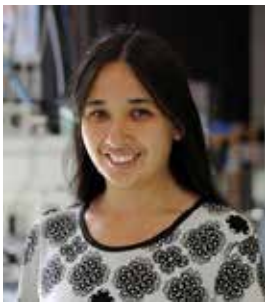
From the scientific perspective, the use of simulation with a VR-helmet allows to understand how the patients' perception of objects and the surrounding space changes over time, which broadens the experience of rehab specialists and they better understand the specific features of RPS use and speak the same language with the patient.

Biography: Director of the Scientific and Industrial Laboratory Sensor Technology for Deaf-blind (Laboratory "Sensor-Tech") Mr. Denis Kuleshov graduated from Bauman Moscow State Technical University with an engineering degree in 2011. Since 2010 Denis Kuleshov has been working at the Centre for Complex Rehabilitation of the Deaf and Hard-of-Hearing Bauman Moscow State Technical University. In 2015 along with partners Mr. Kuleshov established a non-profit organization Development Center of Social Innovation where he holds a position of Director for Science and Innovation.

Since 2017 Mr. Kuleshov has been in charge of Laboratory "Sensor-Tech" established on the initiative of the Deaf-Blind Support Foundation "Con-nection". The Laboratory seeks to develop new technologies, devices and other means of rehabilitation for people with hearing and visual disabilities. In June 2017 the Laboratory in cooperation with partners successfully organized and carried out the first retinal implant surgeries in Russia.

Biography: Medical Projects Lead at Laboratory "Sensor-Tech" Andrey M. Demchinsky, PhD, Ophthalmologist, Medical Projects Lead at the Laboratory "Sensor-Tech".Postgraduate education: The S. Fyodorov Eye Microsurgery Federal State Institution Activities: The first "Argus II" retinal prosthetics system implantations project in the Russian Federation; Two genetic projects to study Usher syndrome and RPE65-associated Retinitis pigmentosa; SeMyWorld ophthalmic simulator project to imitate different symptoms of eye disorders ("SMW VR" for PC and "SMW Pro" for mobile versions); training system for blind football players project to enhance available sensor systems of them

Biography: President of the Deaf-Blind Support Foundation "Con-nection" Mr. Dmitry Polikanov, Ph.D. graduated with honors from the Moscow State Institute of International Relations (MGIMO) of the Russian Ministry of Foreign Affairs in 1998, and a year later got his Ph.D in Political Science. Mr. Polikanov holds the title of Associate Professor from the Russian Academy of Sciences, a position of Associate Professor at MGIMO and the Presidential Russian Academy of National Economy and Public Affairs (RANEPA).
Since 2014 Mr. Polikanov is in charge of the Deaf-Blind Support Foundation "Con-nection". The Foundation has been established with a view to providing support to persons with simultaneous hearing and visual impairments. The Foundation Mission is to become an intermediate between the world of deaf-blind people and the world of people who can see and hear.



Jessica Kvansakul, M.Sci. (Hons), Ph.D.
Bionic Vision Technologies
East Melbourne, Australia

Sensory Substitution to Aid Training with Retinal Prostheses

Jessica Kvansakul1,2, Lachlan Hamilton1, Lauren N. Ayton3,4,5, Chris D. McCarthy6, Matthew A. Petoe1, 2, 1. Bionics Institute, East Melbourne, VIC, Australia 2. Department of Medical Bionics, University of Melbourne, Parkville, VIC, Australia 3. Centre for Eye Research Australia, Department of Surgery (Ophthalmology), University of Melbourne, Melbourne, VIC, Australia 4. Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, VIC, Australia 5. Department of Optometry and Vision Sciences, University of Melbourne, Melbourne, VIC, Australia 6. Department of Computer Science and Software Engineering, Swinburne University, Hawthorn, VIC, Australia

Purpose: Retinal Prosthesis patients with severe vision loss from inherited degenerative retinal disease require extensive training due to the non-intuitive nature of phosphene perception. The aim of this study was to investigate whether the addition of auditory cues, using the Seeing With Sound (SWS) software program, could improve phosphene interpretation for subjects using a real patient phosphene map for simulated phosphene vision (SPV).

Methods: Forty normally sighted subjects completed two visual tasks under three different conditions. The first condition used an SPV algorithm to convert the input camera image to simulated phosphenes displayed on a virtual reality headset. The layout of the displayed phosphenes was non-uniform and based on behavioral measures from a patient implanted with the Bionic Vision Technologies prototype suprachoroidal retinal implant (2012 to 2014). The second condition used the SWS program to provide auditory information of the image via stereo headphones. The program translated the image into sound, scanning from left to right, with horizontal information converted to time, vertical converted to pitch, and intensity converted to loudness. The final condition used both SPV and SWS in combination. The tasks were a light localization task from the Basic Assessment of Light and Motion (BaLM) and the Tumbling-E acuity task from the Freiburg Acuity and Contrast Test (FrACT).

Results: Light localization results showed best accuracy for the combined SPV + SWS condition (94.7 ± 5.8%) which was significantly better than with SPV alone (91.7 ± 9.0%) or SWS alone (89.0 ± 13.0%). Visual acuity results showed that both the SWS condition (0.337 ± 0.041 cpd) and the combined SPV + SWS condition (0.274 ± 0.035 cpd) were significantly better than acuity with SPV alone (0.087 ± 0.002 cpd). Response time results were faster for SPV alone (6.6 + 3.4s) and SPV +SWS (6.7 + 3.1s) compared to SWS alone (9.3 + 4.3s).

Conclusion: Subjects found SPV more intuitive to use, which was reflected in slower response times when SWS was used alone. The response time for the combined condition was not significantly slower than SPV alone, suggesting that SWS is still a viable technique when used in conjunction with SPV. The results did show that combining the SWS and SPV algorithms improved both light localization and optotpye recognition performance, suggesting that there may be a benefit to including auditory cues such as SWS when training visual prosthesis recipients.

Biography: Dr Jessica Kvansakul is a researcher interested in visual perception, biomedical devices and optics. She has an M.Sci, in physics from Imperial College London, and a Ph.D. in Optics and Vision Science from City, University of London. In 2005 she moved to the University of Melbourne, and worked on a range of projects in the optics and vision science areas. Her research interests have spanned optical modelling of surfaces for novel projection screens, laser speckle analysis of artworks and cultural materials, visual perception and colour vision. Jessica is currently a research fellow at the Bionics Institute in East Melbourne and is working on the Bionic Vision Technologies bionic eye project as part of the visual psychophysics group.

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

Optimization of Micro-coil Designs for Selective Cortical Stimulation.

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Purpose: Electrical stimulation via intracortical electrodes has the potential to restore vision to those suffering from a wide range of visual impairments. However, the effectiveness remains limited in part due to the inability of conventional electrodes to selectively activate specific sub-populations of cortical neurons as well as the complex biological reactions that diminish the viability of electrodes over time. Recent demonstrations that magnetic stimulation from a micro-coil can selectively activate vertically-oriented cortical pyramidal neurons (PNs) while avoiding horizontal passing axons suggest the possibility that a coil-based approach may overcome some of those limitations. Here we describe novel micro-coil designs for enhancing selectivity and demonstrate the effectiveness via a series of electrophysiology experiments.

Methods: A computational model was developed to predict the magnetic and electric fields induced by conventional electrodes as well as by rectangular-, V- and W-shaped coil designs. The more promising designs (V- and W-shapes) were fabricated for use in electrophysiological experiments including in vitro patch-clamp recording & calcium imaging (GCaMP6f) of mouse brain slices.

Results: Both V- and W-shaped coils reliably activated layer 5 PNs but V-coils were more effective while W-coils were more selective. Activation thresholds with double-loop coils were approximately one-half those of single-loop coils, regardless of the design. Calcium imaging revealed that both V- and W-coils better confine activation than the conventional electrodes.

Conclusions: Our results suggest that individual design features of micro-coils can influence both their strength as well as their selectivity. Further, our results also suggest that computer simulations based on electromagnetic theory can provide accurate predictions of physiological results. In summary, our results show how coil design influences the response of cortical neurons to stimulation and are an important step towards the development of next-generation cortical prostheses.

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.

Yu Liu, Ms.c
Newcastle University
Newcastle, United Kingdom

Optogenetic Visual Cortical Prosthesis

Dr Soltan, Mr Yu Liu, Dr Nabeel Fattah, Dr Patrick Degenaar, Neuroprosthetics lab, Newcastle University. Additional contributions from the Institute of Neuroscience, Newcastle University (Schmid, Thiele labs), and the wider CANDO project team at Newcastle, UCL, Imperial College.

Abstract: Glaucoma or trauma. Although this is a larger market, the technical and medical challenges mean that there has been very limited clinical progress since the early trials in the 1960s, despite concerted efforts by groups in the field. Although there is now some strong pre-clinical progress in electronic approaches, there are nevertheless some advantages to exploring an optogenetic approach to cortical prosthetics:

1. Genetic methods allow for specific targeting of inhibitory and excitory cells in the cortex
2. Having a different (optical) modality for stimulation makes it easier to perform simultaneous electrical recording to look at efficacy

However, there is considerable complexity in bringing a joint gene therapy and prosthetic system to clinical trials. Furthermore, should there be a negative reaction to either the implant or the gene therapy, resection of a part the visual cortex could be considered harmful, even to those who are blind.

As such, we have a clinical pathway which will target epilepsy first (for which resection of the seizure focus is a current clinical treatment). In that sister project (called CANDO), the objective is to use a combination of optogenetics and optoelectronic brain implants to silence abnormal activity. In parallel in our OptoViS project, we are adapting the technology - both the implant and control unit for the specific needs of cortical prosthetics.

Our clinical solution comprises of a gene therapy component (virus to express the photosensitization agents), a brain implant unit comprising a series of penetrating optoelectronic shafts into the visual cortex, a control unit which includes wireless power/data transfer and local control, and a headset with image acquisition and processing. The general architecture, testing status and clinical pathway will be presented at the conference.

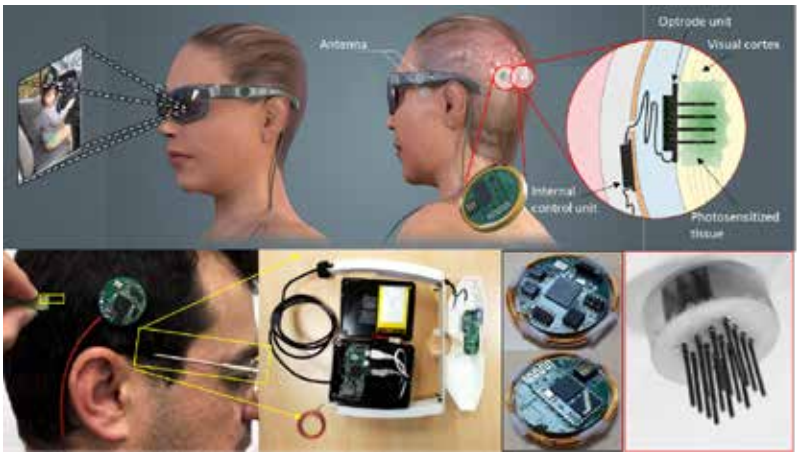
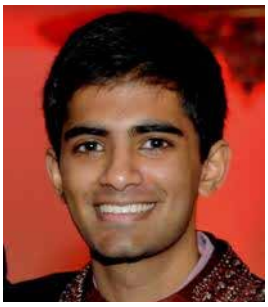


Fig. 1. (top) The 3D concept image of a full wireless multi-colour optogenetics visual cortex implant prosthesis. (bottom, left to right) The implantable control unit, the exemplar headset and external unit, and the optrode array from the CANDO project.

Biography: Yu received his B.Eng. degree (Automation & Control) from Jilin University, China, and MSc. 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.



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Using Electrical Images to Predict Electrical Receptive Fields for Eepiretinal Stimulation

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Objective: To produce high-fidelity artificial vision, epiretinal stimulation of RGCs must be precisely tuned to activate target cells without activating other cells. One approach is to record RGC activity while stimulating, to establish the stimulation thresholds for all cells and electrodes. However, as implants with many closely-spaced electrodes are developed, these measurements become increasingly difficult to analyze. A possible solution is to record, for each cell, the spatiotemporal voltage pattern produced across the array by RGC firing (electrical image, EI) in spontaneous activity, and then to use the EI to infer the thresholds for electrical stimulation over space (electrical receptive field, ERF). Specifically, because the EI for each cell is related to its location, cell type, and geometry, it is possible that it can be used to predict properties of the ERF.

Methods: RGCs in isolated primate retina were stimulated and recorded using a custom array of 512 electrodes (60μm pitch, 8-15μm diameter, in a 16 × 32 isosceles triangular lattice arrangement). For electrical stimulation, charge-balanced triphasic current pulses of varying amplitude (0.1 - 4 μA) were delivered on one electrode at a time. Responses to white noise visual stimulation were used to identify spikes and compute the EI for each RGC. EI properties were then used to identify the collection of electrodes that apparently recorded from somatic and axonal compartments. Finally, EIs were matched to electrically evoked signals from each cell and electrode, to assign evoked spikes to particular RGCs and compute their ERFs.

Results: Approximately 1,000 RGC-electrode stimulation pairs were identified from two major RGC types (ON and OFF parasol) in 5 recordings. The relationship between EI and ERF at somatic and axonal electrodes was different, and each was well fitted the appropriate functional form derived from a physical model. On average these fits predicted somatic and axonal stimulation thresholds to within ~20% of their experimentally determined value. The EI-ERF relationship for somatic activation was more variable than for axonal activation.

Conclusions: A systematic relationship between EIs and ERFs can be used to estimate thresholds for electrical stimulation, and may greatly speed the calibration of future epiretinal
implants.

Biography: Sasi Madugula is a 7th year MD/PhD student at Stanford University in EJ Chichilnisky's lab working on electrical stimulation of Retinal Ganglion cells for retinal prosthesis. He is interested in improving the efficacy of stimulating brain-machine interfaces for understanding neural systems and perturbing them."

Akira Masuda, Ph.D.
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Cell-Type Specific Cortical Stimulations by Red-Shift Light with Lens Optics

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Objective: Optogenetic stimulations potentially hold huge promise in the fields of visual prosthetics. One of the most critical advantages is availability of targeting specific neural populations: under genetic tagging and cell-type specific expression methods, selective group of cells can be activated by actions of light-responsive proteins initiated by specific wave-length light exposure. Despite rapid advances in optogenetic tools, potential combinations of cell-types and proteins were not fully tested practically. Stimulating visual cortex has advantages in covering broad range of patients with severe visual impairments, and greater space capacity for stimulation and implantation. We tested two directions of optogenetic stimulation on visual cortex in rats: activating excitatory neurons (type E) and suppressing inhibitory neurons (type I).

Methods: We developed a stimulating system based on a matrix of small luminance emission diodes (LEDs, 8 x 8 pixels in 20 x 20 mm, 2.8 mm pitch, red color) controlled by an open-source microcontroller Ardiuno and two biconvex lenses aimed for collimating luminescence and broader working distance, enabling stimulation from outside brain. To express optogenetic proteins in a cell-type specific manner, we injected AAV-retro-Cre in V2 and AAV-FLEX-chrimsonR (activator) in V1 of wild-type rats or AAV-DIO-eNpHR3.0 (silencer) in V1 of Parvalbmin-Cre knock-in rats. Both optogenetic proteins are responsive to red-shift light which is characterized by higher biological permeability. Silicon probes for high density electrophysiological recording were implanted into V1 measure neural response at cellular level in vivo. Using an open-source spike-sorting technique (Kilosort and Phy), single unit activities were semi-automatically extracted. After 1 month from the viral injections, the response to micro-photo-stimulation and physiological recording were measured.

Results: The stimulation resolution estimated on the surface of brain was around 0.5 - 0.8 mm with relatively remained intensity (>0.1 mW/mm2 at the maximum). We electrophysiologically confirmed photo-evoked responses in both conditions. The number of responsive cells were larger in condition E than I. Notably, the evoked response duration was longer, but response probability was lower in type E condition than type I condition probably due to difference in local network actions between the target cell-types or photo-kinetics among the optogenetic proteins.

Conclusion: The two strategies of optogenetic cell-type specific stimulation can elicit very different V1 excitation at single unit level. The cell-type specific optogenetic methods may provide a variety of applications for visual restoration.

Biography: Akira Masuda is a research assistant professor to Dr. Takahashi Susumu at the Doshisha University, where he conducts optogenetic artificial vision research in rodents. He obtained his B.S. in Engeneering from Osaka City University in 2006. In 2010, he completed his Ph.D. degree in the Department of Brain Science and Engeneering at the Kyushu Institite of Technology in Japan. From 2011 to 2017, as a postdoctoral fellow, he worked on neuroscience research using rodent genetic models in Dr. Itohara's lab collaborating with Drs. Fujisawa, McHugh, and Saido at Brain Science Institue RIKEN, Japan.

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Trade-offs Between Electrode Size and Dynamic Range for Subretinal Prosthetic Planar Stimulating Electrodes.

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Purpose: Vision loss from diseases of the outer retina such as Retinitis Pigmentosa (RP) or Age-Related Macular Degeneration (AMD) are among the leading causes of irreversible blindness in the world today, and remain a major public health problem affecting tens of millions of people worldwide. The goal of retinal prosthetics is to replace the photo-sensing function of photoreceptors lost in these diseases with optoelectronic hardware that stimulates the remaining retinal neurons. While great progress has been made on this front, significant improvements in restored vision remain unrealized. A critical feature of retinal prosthetic function is resolution. In order to increase the functional resolution of prosthetics, the distance between individual stimulating electrodes (pitch) must be minimized. As electrode pitch decreases and electrode density increases the area available for individual stimulating electrodes must also be decreased. While it is appreciated that smaller stimulating electrodes cannot pass as much current as larger ones for the same electrode material, the relationship between stimulating electrode size and neural stimulation threshold and dynamic range is not well understood.

Methods: To address this important question, we have fabricated custom planar stimulating electrode arrays of sputtered iridium oxide film (SIROF) with different size electrodes and pitch to examine how retinal stimulation thresholds and dynamic range of responses vary with the size of individual stimulating electrodes. Using loose-patch recordings we record ganglion cell response to subretinal stimulation in isolated Rd1 and RD10 mouse retina.

Results: Here, we report the threshold and dynamic range of ganglion cell responses during subretinal stimulation with different sized stimulating electrodes in mouse models of RP. We find that the charge delivery needed to make use of the full dynamic range of neural signaling may place limits on the minimum size of stimulating electrode and consequently impact the packing density of subretinal prosthetics for a common stimulating electrode material.

Conclusion: As retinal prosthetics become higher density, electrode size will become an important design constraint on electrical stimulation strategies to drive the full dynamic range of neural responses available.

Biography: Dr. Oesch is an Assistant Research Scientist at the University of California San Diego Department of Psychology and the Jacobs Retina Center at the Shiley Eye Institute, Department of Ophthalmology. Dr. Oesch started his laboratory at UCSD in 2015 after he a postdoctoral fellowship at the National Institute of Neurological Disorders and Stroke at the NIH in Bethesda, MD. Dr. Oesch received his PhD in Neuroscience from the Oregon Health and Science University in Portland OR in 2008. The focus of Dr. Oesch's laboratory is to understand how the early visual system processes visual information in both normal and diseased states, ultimately leading to therapies for blindness and other neurological disorders. To accomplish this, they use whole-cell electrophysiology, physiological imaging, and psychophysical behavioral paradigms in animal models. The laboratory combines these neuroscience techniques the implementation of novel optoelectronic devices and neural stimulation technologies, to address both fundamental basic science questions regarding neurophysiology and visual neuroscience as well as design therapies to cure blindness.

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The Spike Initiation Zone in Mouse ON and OFF Sustained RGCs Scales with Cell Size

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Purpose: The axon initial segment (AIS) is a specialized membrane compartment in CNS neurons that is comprised of densely packed voltage-gated sodium (Nav) and potassium channels (Kv), held in place by a network of structural proteins. Outside the retina, variations in AIS length, location, and composition have been shown to have important implications for neuronal physiology and may be customized to compensate for differences in other morphological features between different cell types. With over 30 different types of retinal ganglion cells (RGCs), it is likely that variations in the AIS similarly help to shape the different spiking patterns across types but this has not been systematically explored. In this study, we investigate the relationship between length, location and composition of the AIS within ON- and OFF-μSustained (μS) cells of the mouse retina and explore how changes in AIS properties correlate to changes in other morphological features. Because the AIS also influences the sensitivity to electric stimulation, our results will help to better understand why individual RGC types each have different sensitivity. Our findings may also lead to stimulation methods that provide selective targeting of individual types.

Methods: Retinal whole-mounts were surgically isolated from Thy-1 GFP mice, fixed in 4% PFA solution for 30 minutes, and subsequently immunostained for AnkyrinG and Nav1.6 to label the AIS, and ChAT to identify the specific sublamina within the inner plexiform layer at which the dendrites of targeted cells stratified. Anatomical measurements and image analysis of confocal scans were performed in NIH Image J/FIJI package, and statistical plotting was done in MATLAB.

Results: Measurements of soma size and dendritic field size revealed that the two scaled linearly in both the ON and OFF sub-populations ($p<0.001$). Both AIS length and location also increased along the same axis ($p<0.001$); thus, large cells had long AISs that were far from the soma. Interestingly however, the ratio of individual Nav components within the AIS remained highly consistent for all cells within a given cell type.

Conclusions: Previous work from our group demonstrated that the AIS in rabbit RGCs represented the region of lowest threshold for electrical stimulation, and further, that variations in AIS length led to threshold differences across cell types. Changes in cell size of μS RGCs are accompanied by a scaling of AIS properties; it is likely that such changes help to maintain consistency in the physiological responses across this cell type. Knowledge of how the AIS varies with cell type may provide insights into neural activation in the retina, including methods to selectively target specific sub-types.

Biography: Vineeth is a Ph.D. candidate in Biomedical Engineering at Tufts University and a member of Shelley Fried's Neural Prosthetics Laboratory within the department of Neurosurgery at the Massachusetts General Hospital – Harvard Medical School. He received his B.S, and M.S in Biomedical Engineering from the Georgia Institute of Technology, and the Rensselaer Polytechnic Institute, respectively. Vineeth's primary research interests lie in better understanding the morphological and biophysical factors which shape the responses of retinal ganglion cells (RGCs) to electric stimulation, and subsequently using this knowledge to develop improved stimulus protocols which target specific RGC sub-types for application within next-generation visual prosthesis devices.

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MEA-Based Classification of Retinal Ganglion Cells for Bionic Vision

Hamed Shabani, Milad Sadeghi, Zohreh Hosseinzadeh, Eberhart Zrenner, Daniel Rathbun

Purpose: Although there has been significant progress in developing retina implants during the last two decades, due to the inability to selectively stimulate different Retina Ganglion Cell (RGC) types, visual perception for retina implant patients remains limited. We hypothesize that different types of RGCs can be selectively activated by deriving stimuli from their different electrical input filters. The input filters of cells are extracted from their response to electrical noise stimulation using the Spike Triggered Averaging (STA) method. To begin testing this hypothesis, we first classify RGC types using a set of visual stimuli and then examine the properties of each cell type's electrical input filters.

Method: In this study we used the data recorded from nine dark adapted retinas of seven adult wild type mice. A 60 channel microelectrode array in contact with the ganglion cell side of the retina was used to record the spiking neural activity of RGCs. The visual stimulation set was adapted from Baden et al. (Nature 2016), including moving bars, contrast and temporal frequency chirps, blue-green color flashes, and spatiotemporal white noise. In order to extract electrical input filters, a sequence of filtered and interpolated Gaussian white noise voltage steps was used. Similar to Baden et al. we used sparse principle component analysis (sPCA) to extract response features to the visual stimuli.

After projecting data into a lower-dimensional space, we assigned each neuron to one of the 75 clusters reported by Baden et al., by finding the highest correlation between a neuron's response and the clustered response data provided by Baden et al.

Results: We recorded visual responses from 426 RGCs. These responses mapped onto about half of the previously described clusters. Despite convolving our spike trains with a filter to create pseudo-calcium traces for correlation with the previous dataset, many of our responses were significantly more transient than previously reported. ON and OFF cells had different electrical input filters as we have previously reported.

Discussion: Adaptation of the Baden et al. methodology for spike trains instead of calcium recordings was partially successful. For better classification results, new cluster definitions should be derived from a large spike train data set. Electrical input filters do appear to vary with RGC type, but more precise cluster definitions are needed to refine this result.

Biography: Dr. Rathbun received degrees in Neuroscience from the University of Texas at Dallas and the University of California, Davis. He studied bionic vision for a decade in Germany under Professor Eberhart Zrenner, a legend in the field. There, he founded the Experimental Retinal Prosthetics Group at the University Eye Clinic of Tuebingen. In late 2018, Dr. Rathbun moved to Detroit to create the Bionics and Vision lab at Henry Ford where he is an Associate Scientist. He studies the language that the eye speaks to the brain to improve prosthetic vision devices. Such devices restore sight to patients blinded by retinal degenerations such as retinitis pigmentosa and macular degeneration. Dr. Rathbun's research applies the study of neural coding in the visual system to: 1) understanding how images are processed in the healthy and degenerating retina; 2) understanding how the retina responds to electrical stimulation; and 3) using this knowledge to advance bionic vision. At Henry Ford, he is establishing the world's first electrophysiology laboratory dedicated to working with human retinal tissue freshly donated by ophthalmology patients.

Hamed Shabani is a Ph.D. student at the Universtiy of Tuebingen, Germany. He received his Master's degree in Biomedical Engineering from Shahed University in Tehran. Afterwards, he worked as a researcher for one year at the Brain Engineering Center in the Institute for Research in Fundamental Sciences (IPM). Currently, he works in Tuebingen's Retinal Prosthetics Group working to develop new electrical stimulation strategies for the purpose of selective activation of retinal pathways.

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Spatially Confined Evoked Responses of Mouse Visual Cortex by Magnetic Stimulation Using Micro-Coils

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Purpose: Electrical stimulation of the cortex has been suggested as a potential treatment for a wide range of neurological disorders. Despite the success in some clinical trials, it has limitations such as unintended activation of the passing axons from distal cortical regions. Magnetic stimulation with micro-coils implanted in the cortex has the potential to overcome the limitations because coils can selectively avoid activation of the passing axons, and thus confine activation to a focal region.

Methods: To test the efficacy of the magnetic stimulation, in-vivo experiments were performed using anesthetized mice. For the recording of the cortical activity (ECoG) in response to electric or magnetic stimulation, a 128-channel recording array was positioned on the surface of the mouse visual cortex (V1). For the stimulation, a micro-coil (or an electrode) was inserted through the hole in the center of the recording array using a micromanipulator. This arrangement allowed us to quantitatively evaluate and compare the spread of activation.

Results: High frequency (200 Hz) trains of both electric and magnetic stimulation elicited cortical responses, although the spatial extent of activation was different for the two approaches. Electric stimulation activated a spatially expansive area of visual cortex, often more than 1 mm from the stimulation site, while the region activated by magnetic stimulation was confined to a focal area around the stimulation site (approximately 300 μm in diameter).

Conclusions: Our findings suggest that magnetic stimulation from an implantable micro-coil can improve the ability to focally activate cortex and thus may offer advantages over conventional electric stimulation from micro-electrodes.

Biography: Sang Baek Ryu received the B.S. and Ph.D. degree in biomedical engineering from Yonsei University, South Korea in 2006 and 2013, respectively. From 2013 to 2015, he worked as an assistant director in the Medical Device Safety Management Division at MFDS (Ministry of Food and Drug Safety, South Korea). Since 2016, he is working as a research fellow in the department of Neurosurgery at Massachusetts General Hospital and Harvard Medical School.

Roksana Sadeghi, M.S.c
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Seeing the Heat – Subject Performance Comparison Between Thermal and Visible Argus II Camera in Scenarios Approximating Real-Life

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Purpose: To simplify the imagery presented to Argus II retinal implant wearers by filtering out information from cold objects using head-mounted thermal camera. We compared the functionality of thermal camera (H) imagery with visible-light camera (V) imagery in scenarios approximating real life that involved warm targets, e.g., locate the presence/absence of people in a room or avoid hot surfaces/objects for safety.

Methods: The data were acquired from four Argus II users in various real-life tasks including mobility, direction of motion, object localization and two distance discrimination tasks for far and near distances with either hot objects or human targets. In all experiments, the accuracy and response time were recorded. D-prime item and person measures were calculated for responses using signal detection theory in an m-alternative forced choice model. Response times were used to calculate the cumulative probability of success over time which then were compared when subjects used the H versus V camera, using the Kolmogorov-Smirnov (K-S) test.

Results: Four Argus II users aged 62-87 agreed to participate in the study and all performed the mobility, object localization, far and near distance discrimination tasks with 24, 40, 60 and 40 randomized trials, respectively, with each camera. Two subjects performed the direction of motion task near the bottom of an escalator by reporting direction of movement of 100 random people passing by with each camera and trials were randomized by left/right inversion of the camera's image. Despite interindividual differences, results demonstrated that subjects' performance was significantly better with H compared to V using d-prime analysis in all tasks ($p<0.005$). K-S testing of the cumulative probability of success showed that significantly less time was spent to respond with H compared to V, yet with higher accuracy ($p<0.005$).

Conclusion: Subjects detected warm objects and people more accurately with H than using V. Even though the visible camera image would have allowed subjects to use cues such as target size to make the discrimination, performance with this camera was much slower and close to chance, presumably due to a larger number of (non-target) phosphenes. The addition of H camera to V camera in the Argus II system may have significant real-life implications for personal safety and social interactions, thereby improving quality of life.

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 University of California in San Francisco and finished her B.Sc. in physics from Sharif University of Technology in Iran, Tehran.

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Biocompatibility and Surgical Feasibility of Epiretinal Prostheses Extended by an Integrated Circuit (IC) Based Optical Capturing via Photodiodes (OPTO-EPIRET)

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Purpose: Retinal degenerative diseases, e.g., retinitis pigmentosa, cause a severe decline of the visual function up to blindness. Treating these diseases still remains difficult, however, implantation of retinal prostheses can help restoring vision. In this study, the biocompatibility and surgical feasibility of a newly developed retinal stimulator (OPTO-EPIRET) was investigated. Within this proposal, our previously used implant is extended by an integrated circuit (IC) based optical capturing, which enables the immediate conversion of the visual field into stimulation patterns and the stimulation of retinal ganglion cells. Biocompatibility of the newly developed structures was initially verified in vitro. In five follow-up controls (1-12 weeks post-surgery), the rabbits were ophthalmologically examined using funduscopy and optical coherence tomography (OCT). After completing the experiments, histological examination was performed to analyze the retinal structure.

Method: In the beginning, the biocompatibility of the OPTO-EPIRET structures was investigated in vitro using L-929 and R28 cells. Here, direct and indirect contact were analysed in terms of cell proliferation, cell viability and gene expression. The surgical feasibility was initially tested by implanting the OPTO-EPIRET structure in cadaveric rabbit eyes. Afterwards, inactive implants were implanted in six rabbits for feasibility and biocompatibility testings in vivo.

Results: Regarding the in vitro biocompatibility, no significant influence on cell viability was detected (L929: < 1.3% dead cells; R-28: < 0.8 % dead cells). The surgery, which comprises phacoemulsification, vitrectomy and implantation of the OPTO-EPIRET stimulator through a 9 mm corneal incision, was successfully established. The implant was fixated on the posterior pole with a retinal tack. Vitreal hemorrhage, retinal tearing or detachment occurred as main adverse effects. Transitional corneal edema caused difficulties in post-surgical imaging.

Conclusion: The OPTO-EPIRET stimulator showed a good biocompatibility profile in vitro and no signs of cytotoxicity. Furthermore, the implantation surgery was shown to be safe and feasible. Further experiments will comprise the functional analysis of the OPTO-EPIRET stimulator by implanting active devices in acute in vivo setting.

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Cortical Activity Elicited by an Epiretinal Prosthesis Using Small Conductive Diamond Electrodes

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1. Graduate School of Biomedical Engineering, The University of New South Wales, NSW 2033, AUSTRALIA
2.The Bionics Institute of Australia, VIC–3002, AUSTRALIA 3.School of Physics, University of Melbourne, VIC – 3010, AUSTRALIA 4.Centre for Eye Research Australia, Royal Victorian Eye & Ear Hospital, VIC – 3002, AUSTRALIA 5.Department of Surgery (Ophthalmology), The University of Melbourne, VIC - 3010, AUSTRALIA 6.School of Electrical and Biomedical Engineering, RMIT University, VIC – 3000, AUSTRALIA 7. National Vision Research Institute, VIC – 3053, AUSTRALIA #These authors have commercial relationships with iBionics, a company in Ottawa, Canada that is developing the diamond bionic eye. However, iBionics were not involved in any way with the research conducted for this study.

Purpose: In present epiretinal prostheses, the stimulator electronics require separate surgical placement to the electrode array. This paper outlines preliminary results from in vivo experiments utilizing a monolithic device containing small ultrananocrystalline diamond electrodes [1].

Methods: A prototype device containing 25 electrodes (120μm2) was acutely implanted in 16 Pentobarbital-anaesthetised cats through a pars plana vitrectomy, with the device attached to the retina using a tack (n = 7) or via a suprachoroidally placed magnet (n = 9). Neural responses to stimulation using biphasic current pulses were recorded in the visual cortex using Utah arrays.

Results: Device attachment to the retina was highly challenging using both approaches despite its small size, and successful (i.e. cortical responses obtained) in 6 and 5 cats using tacks and magnets respectively. Analyses have so far been completed from 4 animals, where a total of 55/66 electrodes were able to elicit cortical activity within an 80 nC charge limit. The mean threshold using a monopolar (MP) return, cathodic-first (CF) pulses and a 500 μs phase width (PW) was 24.2 ± 1.9 nC (Mean ± SEM), and mean cortical spread was 1.2 ± 0.1 mm. There was no difference in thresholds or spread between CF and anodic-first (AF) pulses, however, the former evoked responses with shorter latencies (n = 13; paired t-test; p = 0.021; CF, 8.2 ± 0.5 ms; AF, 9.4 ± 0.4 ms). PW did not influence thresholds or latency (n = 10; 2-way RM ANOVA), however, the choice of return between MP and common ground (CG), influenced both thresholds ($p < 0.01$; MP, 15.3 ± 3.1 nC; CG, 32.5 ± 3.9 nC) and latency (p = 0.001; MP, 7.9 ± 0.2 ms; CG, 10.5 ± 0.5 ms). For cortical spread, the interaction between PW and return was significant (p = 0.023). MP stimulation always resulted in larger spread compared to CG, except for a PW of 500 μs. For a MP return, 500 μs resulted in lower spread compared to 250 μs and 1000 μs. For a CG return, PW had no effect on spread. Dissection and histological analyses revealed retinal damage in all cases.

Conclusions: Both surgical approaches were challenging in terms of atraumatic and reliable attachment to the retina. Return configuration had the greatest effect on cortical responses. Higher resolution was achievable using a CG return, however at the cost of higher thresholds. Overall, the diamond-based device may be a viable epiretinal prosthesis if key surgical and damage issues can be resolved.

Biograpy: Dr Mohit Shivdasani arrived in Australia from India to pursue a Master's degree in Biomedical Engineering at La Trobe University, Melbourne. He was subsequently offered a scholarship to undertake a Ph.D. in Auditory Neuroscience following which he took up a postdoctoral Research Fellow position at the Bionics Institute (formerly Bionic Ear Institute) in 2009. Since then, Dr Shivdasani has been part of a multi-disciplinary team whose research is focused on developing a bionic eye for vision restoration in blind humans through a $50M federally-funded grant awarded to Bionic Vision Australia. Dr Shivdasani's own research at the Bionics Institute played a major role in this project since the beginning, and his unique preclinical electrophysiology experiments were instrumental in the design and development of Australia's first bionic eye prototype which was successfully implanted in three patients in 2012, only 3 years since the development of the device began. Subsequently, he became part of the team performing carefully controlled psychophysical experiments in the implanted patients, and testing strategies to help patients use their implant to its full capability and improve the level of vision attainable. In February 2018, he was appointed as a Senior Lecturer in Bionics in GSBmE, UNSW and began a new life chapter in Sydney after having lived in Melbourne for 15 years. Based on this unique preclinical and clinical experience with the bionic eye his future goals are to continue basic research to help improve the resolution of devices which will help improve functional outcomes and increase the quality of living for patients.

Dr Shivdasani has published several papers in prestigious international journals and has won many awards including the 2006 Young Biomedical Engineer of the Year presented by Engineers Australia. In 2014, he procured independent research funding through a New Investigator Project grant from the National Health and Medical Research Council of Australia and was elected as a Senior Member of the Institute of Electrical and Electronics Engineers (IEEE) in 2016. Dr Shivdasani has also supervised a number of Ph.D. and Master's students to completion and has made numerous local and international invited presentations about his research, both professionally and publicly.

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The Effect of Pulse Durations on the Spatial Resolution of Sub-retinal Stimulation Using a Diamond-Based Retinal Prosthesis

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Purpose: Retinal Prosthesis attempt to treat incurable retinal degenerative diseases by electrical stimulation of surviving neurons in the inner retina (mainly retinal ganglion cells, RGC). Clinical studies indicate that although a sense of vision can be restored, the visual acuity obtained is limited and functional vision, such as navigation and facial recognition remains challenging. One major difficulty is associated with the low spatial resolution obtained from electrical stimulation, i.e. the large spread of activation amongst RGCs leads to blurred or distorted visual percepts. Previously the effect of pulse durations has been studied for epi-retinal stimulation and long pulses (>24ms) were found efficient to confine the activation of RGCs [1]. However, how pulse durations influence the spatial resolution of sub-retinal stimulation remains unknown. Here, we used an electrode array based on a novel diamond substrate and imaged the response of explanted retina to sub-retinal stimulation. The effect of pulse durations is the focus of the study.

Method: A 5x5 diamond-based electrode array with 120μmx120μm electrodes with a pitch of 150um was fabricated as previously described [2, 3]. Electrophysiological data were acquired from adult Royal College Surgeon rats (RCS, >3 months). The RCS rat has inherited retinal degeneration and completely lose their outer nuclear layers after 90 days from birth. Following anesthetics and enucleation, calcium indicator OGB-1 was injected into each eye from the cut end of their optic nerves. After overnight loading, the explanted retina was mounted with RGC side up onto the electrode array and the response was imaged to stimulation using a confocal microscopy. Stimuli were composed of biphasic pulses with pulse duration varying from 33μs up to 24ms.

Results: Figure 1 shows the typical results of RGCs activated with an ultrafast pulse (33μs), a medium length pulse (0.5ms) and a long pulse (24ms). While 0.5ms pulses led to great activation spread due to the activation of axon bundles, 24ms pulses could hardly activate RGCs within the safe charge injection limit of diamond electrodes (1.5mC/cm2). Only 33μs pulses lead to a focal activation with only neurons near electrodes activated.

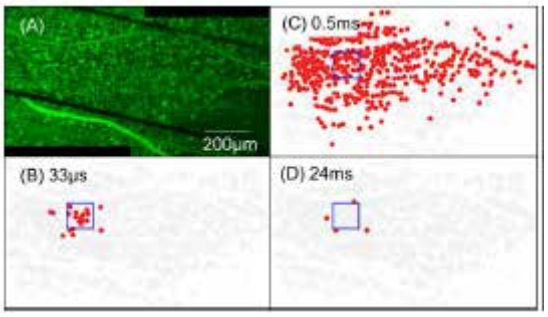

Figure 1. A typical result of rat RGCs in response to sub-retinal stimulation with different pulse durations. All images are orientated that the optic disk lies to the left of the images and axons go to the right. (A) shows the staining of the RGCs and axon bundles. (B)-(D) are the response to pulse durations 33μs, 0.5ms and 24ms, respectively. RGCs with more than 50% response are drawn red while RGCs with no response are open circles. Blue squares indicate the location of the stimulating electrode.

Conclusion Ultrafast pulses (33μs) are the most effective for confining the activation of RGCs for sub-retinal stimulation.

Biography: Dr Wei Tong has a BS degree from University of Science and Technology of China and a Ph.D. from the University of Melbourne, both majoring in physics. She is now a postdoc researcher at the National Vision Research Institute of Australia (NVRI). During the past 7 years, she has been working on the development of a high acuity diamond based retinal prosthesis. Her PhD work focused on the fabrication and optimization of the diamond electrodes. Her current research at NVRI is on the in vitro testing of the diamond devices as well as the development of the stimulation strategies for improving their visual acuity. Her interests and knowledge of neural prosthetics cover various aspects from device fabrication to electrophysiology.

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Phosphene Mapping for Intracortical Visual Prostheses

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Purpose: Intracortical visual prostheses (ICVPs) are a novel class of devices that transmit visual stimuli from an external camera to an electrode array implanted in the visual cortex, thereby eliciting visual percepts (phosphenes) and restoring limited functional vision to the blind. The visual world must be encoded into patterns of electrode stimulation that produce intelligible images, requiring knowledge of where in the visual field each electrode produces a phosphene. This project aims to develop a multi-modality phosphene mapping method for calibration of ICVPs.

Methods: We simulated the perceptual experience of electrode stimulation in an ICVP recipient by displaying phosphenes (points of light) to sighted subjects using a FOVE virtual reality headset. Subjects indicated the position of each phosphene within their visual field by making a saccade or pointing a finger towards the perceived target, and these movements were measured using a built-in eye-tracking feature and a LeapMotion camera, respectively. A set of known points was presented in order to determine calibration parameters for each subject, which were used to apply linear adjustments to the measurements to reconstruct the initial set of points.

Results: Average R2 between presented and reconstructed coordinates were 0.97 and 0.96 for eye tracking and 0.92 and 0.97 for finger tracking in the x and y directions, respectively. By applying linear adjustments, a set of calibration points was recreated with an average root-mean-square error (RMSE) of 0.131 normalized units (figure 1a). Similar methods applied to finger tracking produced maps with an average RMSE of 0.226 (figure 1b).

Biography: Sam Weinreb was born in Manhattan, grew up in Madison, Connecticut, and then returned to NYC to study biomedical engineering and psychology at Columbia University ('17). As an undergraduate, he had an academic focus on neural engineering and imaging as well as a research interest in retinal ganglion cell development. As a now-third-year medical student at Johns Hopkins University, he has published on glaucoma surgical outcomes and is currently working in the Ultra-Low Vision Laboratory to develop a phosphene mapping protocol for The Intracortical Visual Prosthesis Project. Though he has not yet decided on a specific medical specialty, he ultimately hopes to forge a career as a "surgeoneer."

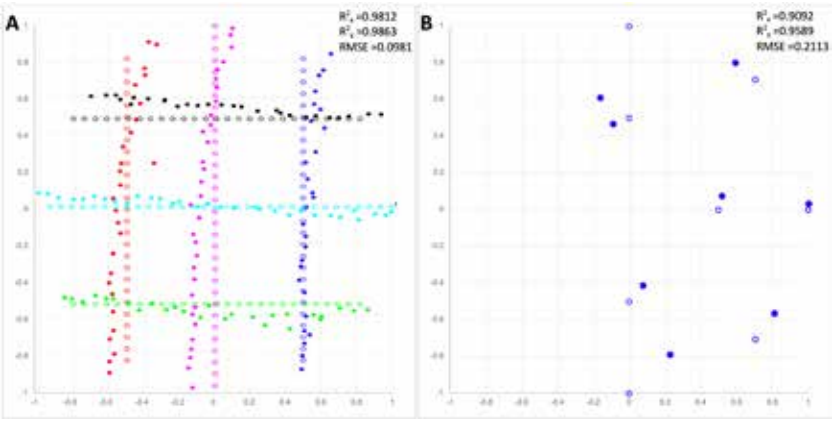

Figure I. Presented (unfilled) and reconstructed (filled) phosphene maps using measurements from eye tracking (a) and finger tracking (b). All units are normalized cartesian coordinates.

Conclusions: Phosphene maps reconstructed by tracking saccades had, on average, less random error and systemic distortion than those produced by tracking finger position. Eye tracking thus appears more promising as a primary method for ICVP calibration, whereas finger tracking may be useful as an adjunct or as a stand-alone phosphene mapping method in individuals without intact eye movements. Next steps include applying nonlinear adjustments to the measurements and integrating data from both modalities with relative mapping of adjacent phosphene pairs.

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Location-Dependent AIS Variations and their Influence on Preferential Activation of RGC Subclasses

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Purpose: Recently, we found that the axon initial segment (AIS) anatomy in alpha retinal ganglion cells (RGCs) of the mouse retina differs depending on retinal location. Since the AIS has been shown to be the key element for direct activation of RGCs by electric stimulation we conducted a series of computer simulations to examine the influence of differential AIS geometry on preferential activation of RGC subclasses depending on retinal location.

Methods: Filled mouse alpha RGCs from various retinal locations were stained for streptavidin, ChAT and AnkyrinG and morphology was reconstructed using confocal microscopy. AIS length and distance from the soma were determined by measuring the length of co-aligned regions of RGC axons and AnkyrinG. Multi-compartment modeling was used to compute the threshold to extracellular electric stimulation in different alpha RGCs subclasses.

Results: As suggested by previous studies activation thresholds were lowest when the stimulating electrode was located close to the AIS. The site of spike initiation, i.e. the location along the neural membrane that triggered an action potential, was still located within the AIS even when the stimulating electrode was located remote of the AIS. Longer AISs tended to have lower thresholds compared to short AISs and comparison of activation threshold of different RGC subclasses within the same retinal locations revealed preferential activation for RGCs with a longer AIS. Preferential activation of a distinct subclass over another (e.g. ON-Alpha sustained vs. OFF-Alpha transient) was not consistent for different retinal locations as their AIS geometries do not vary uniformly.

Conclusions: Our results indicate that preferential activation of distinct RGC subclasses is strongly dependent on retinal location and accompanied AIS variations. Since there is only limited data available on location-dependent AIS variations future studies will be needed to examine if such location-dependency as shown here in mouse retina also translates into higher order species and/or human retina.

Biography: Paul is currently a Senior Postdoctoral Research Fellow in Frank Rattay's lab 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.

Varalakshmi Wyuyyuru, M.S.
Second Sight Medical Products
Sylmar, California

Single-Electrode Perceptual Thresholds for the Orion™ Visual Cortical Prosthesis System

Varalakshmi Wuyyuru1, Uday Patel1, Michelle Armenta Salas1, Soroush Niketeghad2, William Bosking3, Michael P. Barry1, Daniel Yoshor3, Jessy Dorn1, Nader Pouratian2 1Second Sight Medical Products, Inc. 2University of California, Los Angeles, Department of Neurosurgery 3Baylor College of Medicine

Purpose: The Orion Visual Cortical Prosthesis holds the potential for restoring some vision to individuals who have completely lost their vision due to any non-cortical reason. Six patients were enrolled in the Orion early feasibility study at two centers, University of California, Los Angeles and Baylor College of Medicine. The Orion implant electrode array consists of 60 non-penetrating electrodes with 2mm diameter separated by 3 mm center to center electrode distance. Single electrode thresholds are a primary input to the individualized program that converts visual information into stimulation patterns.

Methods: Thresholds, defined as the minimum current required to elicit a well-defined percept, is determined for each electrode using a Binary Search method. Testing for all electrodes start at 500 μA, with pulse width per phase set to 0.28 ms. the amplitude is limited at the higher end by the maximum safe charge limit of 1.5 μC/phase, or by the maximum current the device can generate of 7.5 mA, whichever comes first. The smallest amplitude tested will be the minimum current the device can generate, 32.3 μA. The thresholds were measured at 20 Hz frequency and at 40 μs Inter phase gap with cathodic-leading charge-balanced square wave pulse train, 250 ms in duration. 5 -10 electrodes were selected at different parts of the array for four patients and thresholds were monitored until 12-months post-op period.

Results: 97% of active electrodes elicited thresholds across all six patients. The average thresholds ranged from 1.6 mA - 3.7 mA with average standard deviation of 1.1 mA at the first measurement. Threshold trend over time is consistently stable over time across the four patients.

Conclusions: Stability of the perceptual thresholds over time in Orion patients is encouraging even after chronic use of the device at home (2 hours/day maximum). This could be due to relatively bigger Orion electrodes generating reliable and consistent phosphenes. Also this assures that the new binary search method is reliably measuring the thresholds. We continue to monitor the perceptual thresholds to determine if any known or unknown factors that may impact them over time.

Biography: Vara Wuyyuru is a Senior Clinical Scientist at Second Sight Medical Products working in the field of artificial vision for over 12 years. She works with Argus 2s and Orion patients to understand the kind of vision that they are receiving from retinal and cortical visual prostheses. Her work includes creating new technologies, psychophysics approaches and innovative training methods to improve the patients' visual perception and thus improve their quality of life. Her ambition resonates with the Second Sight's mission of creating an artificial form of useful vision to profound blind individuals.

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Shelly Fried, Ph.D. accepting the Bartimaeus Award from Edward O'Malley, M.D. in 2017. Accompanied by previous Bartimaeus recipients.

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