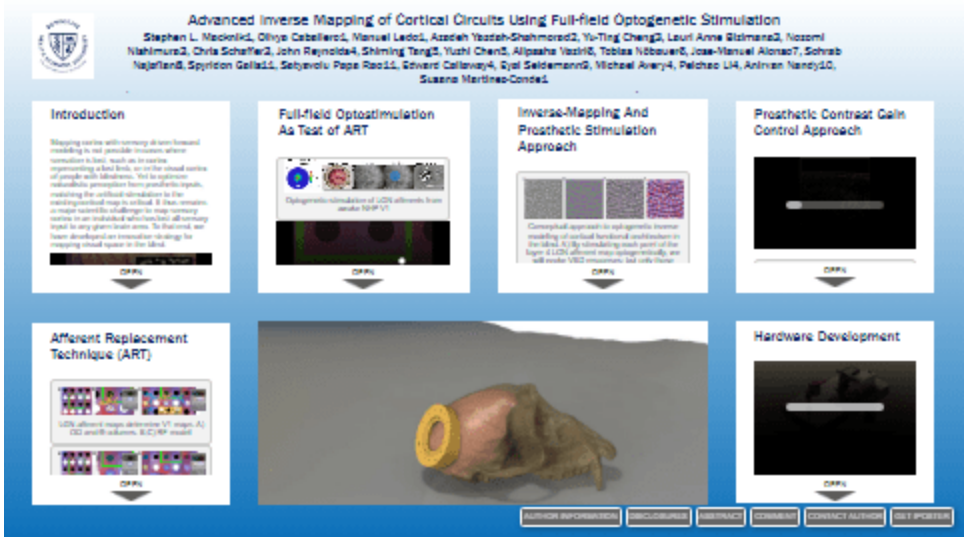
Advanced Inverse Mapping of Cortical Circuits Using Full-field Optogenetic Stimulation



Stephen L. Macknik1, Olivya Caballero1, Manuel Ledo1, Azadeh Yazdah-Shahmorad2, Yu-Ting Cheng3, Lauri Anne Bizimana3, Nozomi Nishimura3, Chris Schaffer3, John Reynolds4, Shiming Tang5, Yuzhi Chen5, Alipasha Vaziri6, Tobias Nöbauer6, Jose-Manuel Alonso7, Sohrab Najafian8, Spyridon Galis11, Satyavolu Papa Rao11, Edward Callaway4, Eyal Seidemann9, Michael Avery4, Peichao Li4, Anirvan Nandy10, Susana Martinez-Conde1

1SUNY Downstate Medical Center, Brooklyn, NY; 2University of Washington, Seattle, WA; 3Cornell University, Ithaca, NY; 4Salk Institute for Biological Studies, La Jolla, CA; 5Peking University, Beijing, China, 6The Rockefeller University, New York, NY, 7SUNY Optometry, New York, NY, 8Harvard Medical School, Boston, MA 9University of Texas, Austin, TX; 10Yale School of Medicine, New Haven, CT

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INTRODUCTION

Mapping cortex with sensory driven forward modeling is not possible in cases where sensation is lost, such as in cortex representing a lost limb, or in the visual cortex of people with blindness. Yet to optimize naturalistic perception from prosthetic inputs, matching the artificial stimulation to the existing cortical map is critical. It thus remains a major scientific challenge to map sensory cortex in an individual who has lost all sensory input to any given brain area. To that end, we have developed an innovative strategy for mapping visual space in the blind.

[VIDEO] https://res.cloudinary.com/amuze-interactive/video/upload/vc_auto/v1685931640/infinity/C6-69-C9-5A-22-5C-97-71-6F-A8-6F-8A-9E-0C-5A-8D/Video/Healthy_Vision_Overview_nauljz.mp4

FULL-FIELD OPTOSTIMULATION AS TEST OF ART

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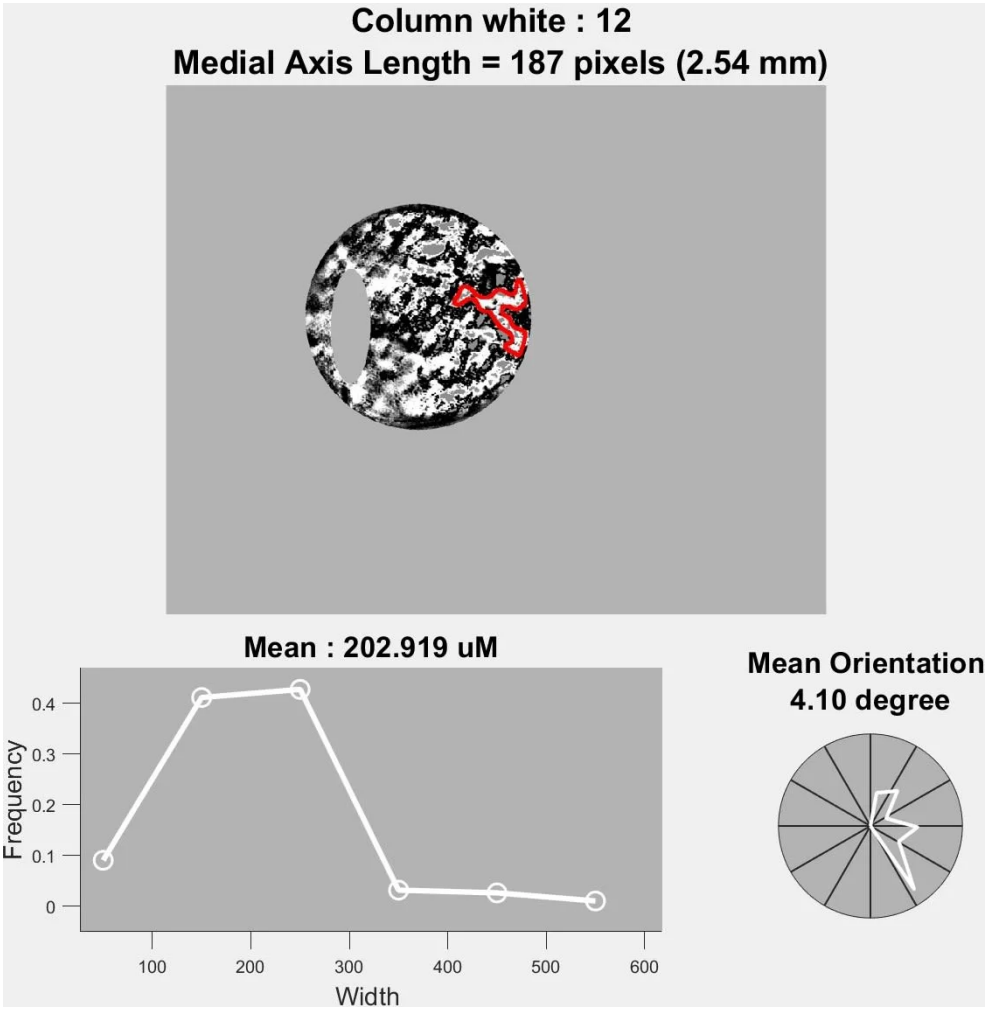
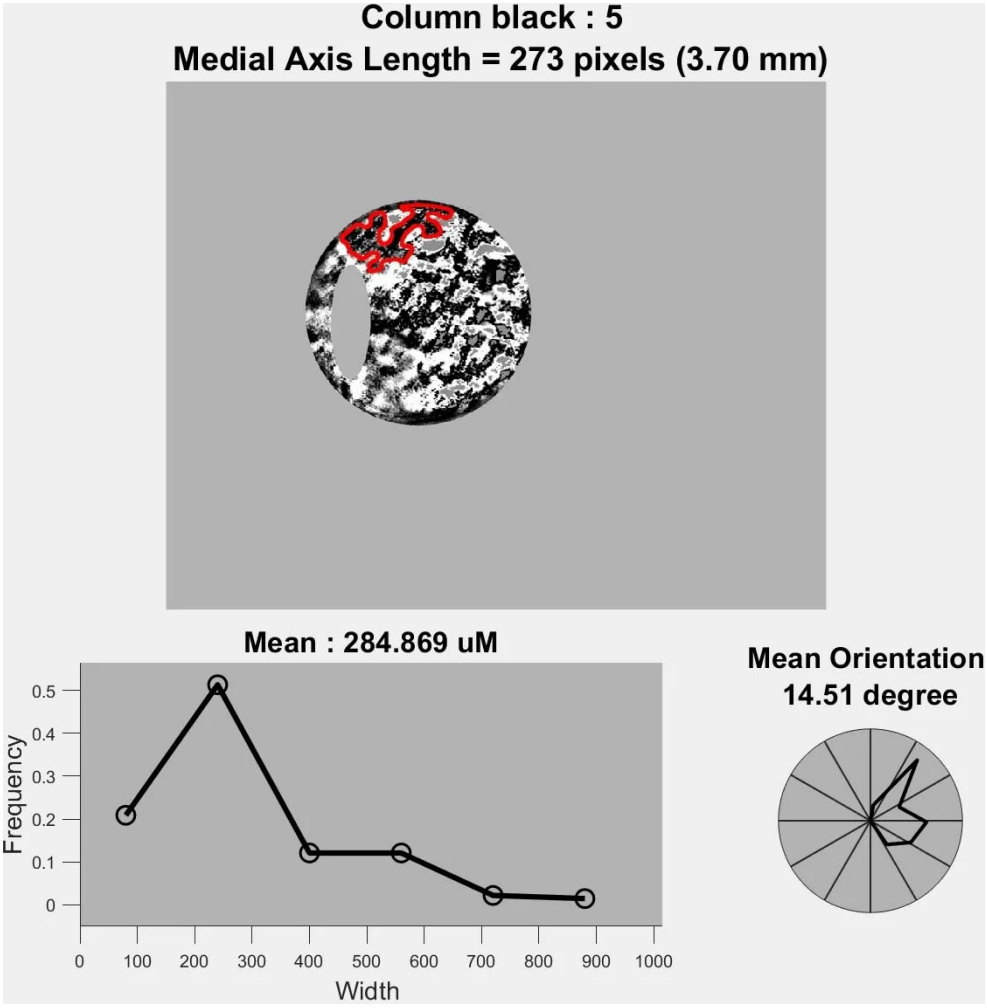
Optogenetic stimulation of LGN afferents from awake NHP V1

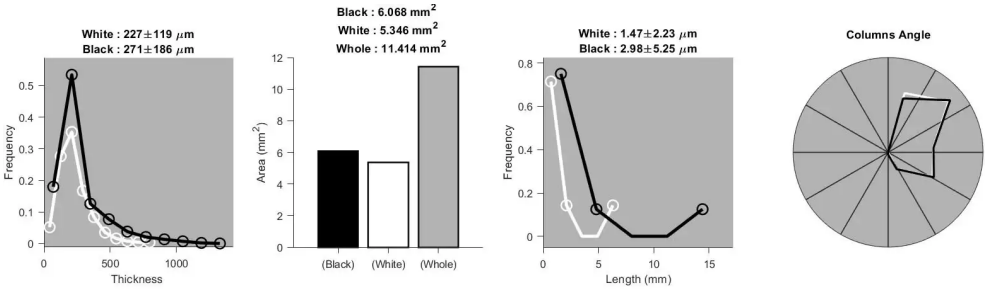
[VIDEO] https://res.cloudinary.com/amuze-interactive/video/upload/vc_auto/v1685920110/infinity/C6-69-C9-5A-22-5C-97-71-6F-A8-6F-8A-9E-0C-5A-8D/Video/zemax_scatter_model_kc890r.mp4



White Columns Size Is Predicted By ART

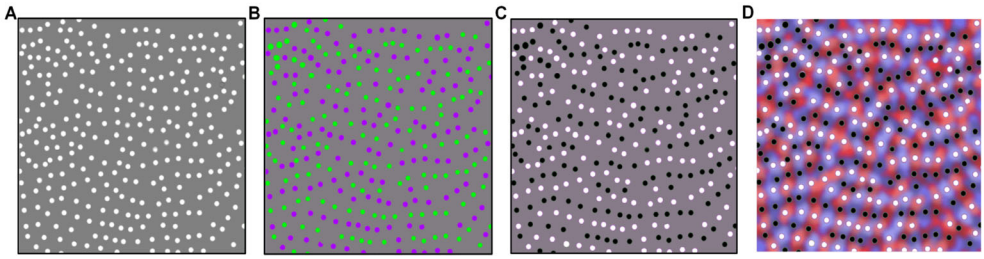


Black Columns Size & Θ Predicted by ART

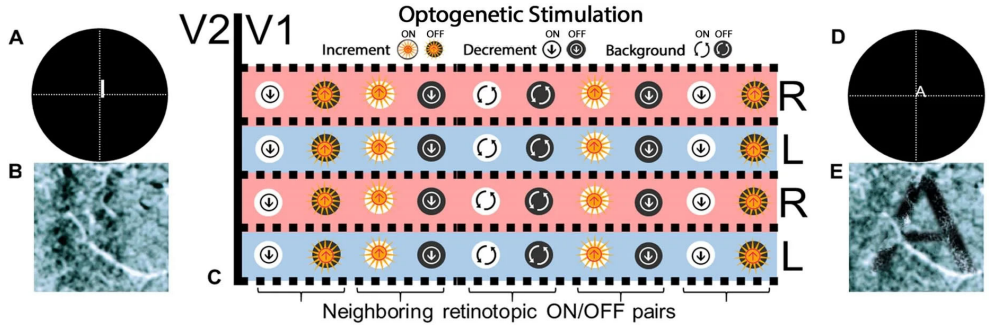


Population Analysis of Full Field OptoStim

INVERSE-MAPPING AND PROSTHETIC STIMULATION APPROACH



Conceptual approach to optogenetic inverse modeling of cortical functional architecture in the blind. A) By stimulating each point of the layer 4 LGN afferent map optogenetically, we will evoke VSD responses: but only those points at the center of a layer 4 ON and OFF afferent input domain will generate strong responses (other points will cancel or weaken due to ON and OFF intermixing and splitting stimulation across OD columns). This map will not indicate the contrast-sign of the columns, however. B) By conducting reverse-correlation mapping with a optimized spatiotemporal optogenetic mapping stimuli, we will identify which of these points share the same contrast-sign, though we will not yet know which population indicates ON vs OFF to the NHP. C) Patterning (and other) clues will guide the mapping. For example, because OFF columns are known to be more numerous than ON columns, we can assign OFF vs ON contrast-signs if we determine a difference in numerosity. D) The fundamental patterning and spacing of the ON and OFF columns will be used to determine the OD organization. Further, because layer 4 afferent fields are oblong in the axis along the OD columns , they have paired and mutually inhibitory ON and OFF columns sharing the same retinotopic positions. They also run perpendicular to the ON and OFF stripes in Panel C, which we can further exploit to determine the OD column map.



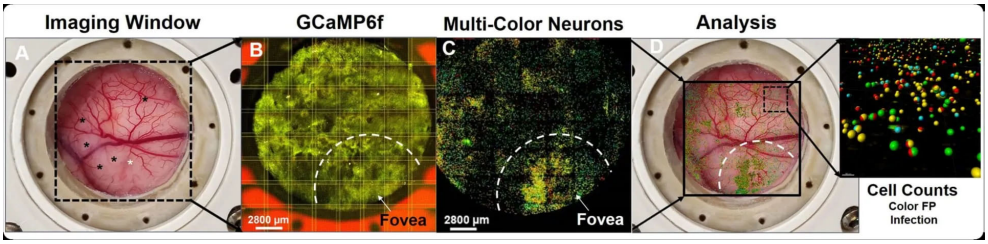
A) A vertical line stimulus, presented at the fovea. B) Macknik lab preliminary data 1 of intrinsic signal optical imaging of a 1 cm2 field in V1 recorded from an NHP. V1 activates to the two edges of the vertical line segment as if they were individual stripes (one for each edge of the line). Note that intrinsic signal (same physiological mechanisms as BOLD) does not differentiate between ON and OFF responses, whereas our model will. C) A cartoon of the hypothesized ON and OFF column activities within the Layer 4 LGN afferent map. D) If we were to present a letter ‘A’ optogenetically—at the resolution of a typical New York Times newspaper font—our model 1 suggests that the optogenetic stimulation would produce a VSD pattern simulated in E).

[VIDEO] https://res.cloudinary.com/amuze-interactive/image/upload/f_auto,q_auto/v1685896105/infinity/c6-69-c9-5a-22-5c-97-71-6f-a8-6f-8a-9e-0c-5a-8d/image/shapefromedges_ticlnk.mp4

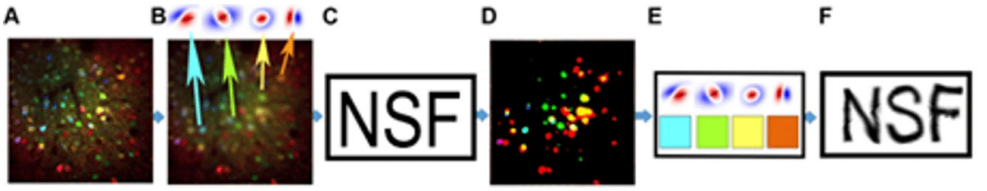
Patterned inputs to targeted Θ and OD afferents will drive shape perception

PROSTHETIC CONTRAST GAIN CONTROL APPROACH

[VIDEO] https://res.cloudinary.com/amuze-interactive/video/upload/vc_auto/v1685921098/infinity/C6-69-C9-5A-22-5C-97-71-6F-A8-6F-8A-9E-0C-5A-8D/Video/Bioluminescence_Gain_Control_Approach_tjl8pa.mp4

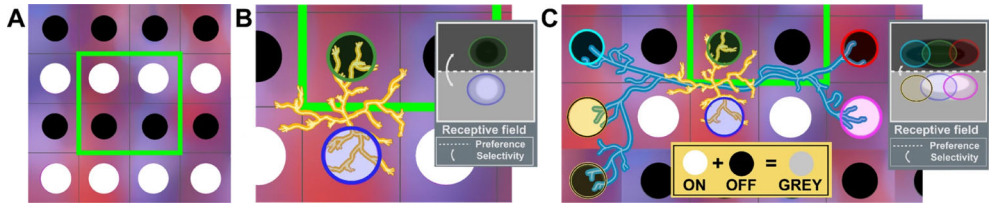


Prosthetic contrast gain control can be achieved through bioluminescent readout

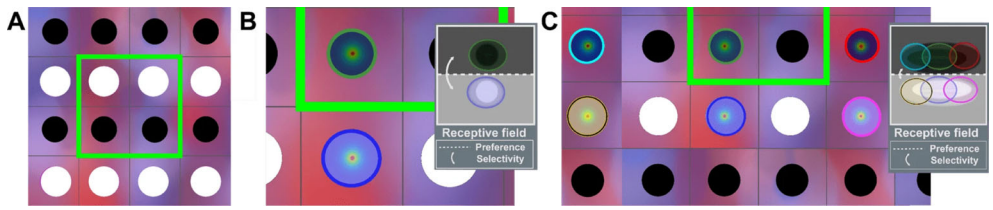


Bioluminescent brainbow labeling allows spatiochromatic mapping

AFFERENT REPLACEMENT TECHNIQUE (ART)



LGN afferent maps determine V1 maps. A) OD and Θ columns. B,C) RF model



Targeted optostimulation of LGN afferents can replace natural inputs.

HARDWARE DEVELOPMENT

[VIDEO] https://res.cloudinary.com/amuze-interactive/video/upload/vc_auto/v1685929736/infinity/C6-69-C9-5A-22-5C-97-71-6F-A8-6F-8A-9E-0C-5A-8D/Video/Monkey_Rig_development_p8upbi.mp4
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[VIDEO] https://res.cloudinary.com/amuze-interactive/image/upload/f_auto,q_auto/v1685930317/infinity/c6-69-c9-5a-22-5c-97-71-6f-a8-6f-8a-9e-0c-5a-8d/image/neurophotonics_vo3q9h.mp4
Coplanar emitter/detector dyad nanophotonic chip with 128 μm pitch

[VIDEO] https://res.cloudinary.com/amuze-interactive/image/upload/f_auto,q_auto/v1685930996/infinity/c6-69-c9-5a-22-5c-97-71-6f-a8-6f-8a-9e-0c-5a-8d/image/chamber_twjm7k.mp4
Preclinical NHP development of surgical implant methods and materials

[VIDEO] https://res.cloudinary.com/amuze-interactive/image/upload/f_auto,q_auto/v1685931228/infinity/c6-69-c9-5a-22-5c-97-71-6f-a8-6f-8a-9e-0c-5a-8d/image/human_implant_hardware_iebwrv.mp4
Human implant hardware derives from the NHP hardware and materials we developed, to position the photonics chip against the foveal V1 cortex, while receiving real-time input and control from the eye-tracking glasses.

DISCLOSURES

Most of the innovations described here have been declared as intellectual property of SUNY and its collaborators with the intention of achieving patent protection. This work was supported by the New York State Empire Innovator Program, the National Science Foundation (Award 1734887 to SM-C and SLM), and the National Institute of Health (Awards R01EY031971 to SM-C and SLM, and R01CA258021 to SM-C and SLM).

AUTHOR INFORMATION

Stephen L. Macknik[1], Olivya Caballero[1], Manuel Ledo[1], Azadeh Yazdah-Shahmorad[2], Yu-Ting Cheng[3], Lauri Anne Bizimana[3], Nozomi Nishimura[3], Chris Schaffer[3], John Reynolds[4], Shiming Tang[5], Yuzhi Chen[5], Alipasha Vaziri[6], Tobias Nöbauer[6], Jose-Manuel Alonso[7], Sohrab Najafian[8], Spyridon Galis[11], Satyavolu Papa Rao[11], Edward Callaway[4], Eyal Seidemann[9], Michael Avery[4], Peichao Li[4], Anirvan Nandy[10], Susana Martinez-Conde[1]

[1]SUNY Downstate Medical Center, Brooklyn, NY; [2]University of Washington, Seattle, WA; [3]Cornell University, Ithaca, NY; [4]Salk Institute for Biological Studies, La Jolla, CA; [5]Peking University, Beijing, China, [6]The Rockefeller University, New York, NY, [7]SUNY Optometry, New York, NY, [8]Harvard Medical School, Boston, MA [9]University of Texas, Austin, TX; [10]Yale School of Medicine, New Haven, CT

TRANSCRIPT

ABSTRACT

The development of optogenetic technology for the restoration of vision in blind patients has gained significant attention in recent years. The Optogenetic Brain System (OBServ) is an integrated nanophotonic implantable device that aims to restore foveal vision in the blind by mimicking naturalistic visual input patterns. By transducing lateral geniculate nucleus (LGN) neurons with light-sensitive proteins, the system can optogenetically stimulate these purely glutamatergic inputs without unwanted co-activation of inhibitory neurons, resulting in maximal contrast sensitivity. This system is designed to function by optimally activating optogenetically transduced LGN afferents entering the primary visual cortex (V1), driven by a fully-implantable coplanar neurophotonic emitter-detector array, that reads out activity from cortical cells transduced with genetically encoded bioluminescence genes. By targeting spatially localized LGN synaptic boutons that have been mapped and identified for their specific function, naturalistic vision can be restored by providing a pattern of stimulation that mimics natural visual input. Here we show evidence suggesting that mapping of ON/OFF fields can be partially achieved using full field stimulation of the LGN bouton field, to result in interdigitated stripes of V1 activation derived from the mutual antagonism of ON/OFF submodules shared by the same hypercolumn: The full-field stimulation is suppressed along the border of ON and OFF columns that interact with each other in the upper layers of cortex (i.e. because they occupy the same hypercolumn), whereas the fully activated stripes indicate the border zones between ON/OFF columns of neighboring hypercolumns. OBServ will target specific submodules within targeted hypercolumns to account for rapidly changing cortical activity and gain control with a real-time cortical read-out mechanism. This is achieved by reading-out a multi-colored array of genetically-encoded and transduced bioluminescent calcium responses in V1 neurons, which can achieve single-cell resolution. OBServ will track eye movements in the blind patients to account for oculomotor effects by adjusting the contemporaneous stimulation of the LGN boutons to mimic the effects eye movements. This prosthetic technology does not cross the pia mater of the brain and holds the promise of restoring vision in the blind at the highest attainable acuity, with maximal contrast sensitivity.