Retina Australia Report - Improving the global acceptance of retinal prostheses: Assessing the influence of different stages of retinal degeneration on selective activation of retinal ganglion cells.

Our vision is interpreted by a more than a dozen functionally-distinct retinal visual pathways. Each visual pathway detects unique features from visual inputs, and only transmits specific information to the brain through distinct and precise patterns of spiking activity. Although these channels can be selectively stimulated under natural vision, it is extremely challenging to discriminate them under artificial electrical stimulation due to the differential mechanism of neural excitation under natural and electrical stimulation. This in turn sends conflicting information to the brain leading to poor artificial vision. Our team pioneered the use of novel stimulation paradigms to achieve differential activation of visual pathways in the retina. We demonstrated that functionally-different retinal pathways, those that form part of the ON pathway (signals increase with increasing light intensity) and those forming part of the OFF pathway (signals decrease with increasing light intensity), can be selectively activated by appropriately varying different stimulus parameters. Building on and generalising beyond these initial studies, this Retina Australia project extended our research by answering two questions: *1) how well can selectivity be achieved for more specific pathways?* And *2) to what degree does the remodeled neural network mediate the performance of electrical stimulation?*

As a first step in answering these questions, we conducted *in vitro* investigation. Retinal pathways were further classified into transient (ON-Transient and OFF-Transient) and sustained (ON-Sustained and OFF-Sustained) pathways. Sustained pathways are reported to detect form, size and shape, and transient pathways detect the motion or location in human vision. The ability of controlling these pathways using electrical stimulation is critical to generate artificial vision. We found three tested visual pathways (ON-Transient, OFF-Transient and OFF-Sustained) demonstrate their characteristic stimulus-frequency-dependency, and can be preferentially controlled in their specific stimulus parameter space. indicating the identifiability of more specific pathways from the electrically-modulated retina.

As the second part of this study, we conducted *in vitro* experiments in different stages of animal models of retinal degeneration coupled with detailed immunohistochemistry techniques to analyse correlations between the effectiveness of electrical stimulation, and key functional/anatomical retinal changes. While this study is still on-going, our preliminary results suggest the possibility of differential activation in degenerated retina, but with a re-optimised stimulation parameter space. We are currently extending these results across multiple stages of degeneration and across a broader range of stimulation amplitudes and frequencies. All results from this grant will be useful in studying the patterns of electrical pulses from artificial stimulation on the retina and speedup the design and development of next-generation retinal implants, and in doing so, significantly improve the quality-of-life for bionic eye recipients.

This grant has resulted in multiple publications both published and submitted. Some proof-of-concept results [1] have been submitted to be presented in 2020 Annual International Conference of the IEEE, Engineering in Medicine and Biology Society (EMBS), the world's largest international society of biomedical engineers. In addition, we have recently submitted two manuscripts to a high impact, Journal of Neural Engineering, Special Issue on The Eye and the Chip [2, 3].

Moreover, we successfully applied travel funding to attend major international conferences, and leading research institutes, to dissemination of new results to the wider research community as well as strengthen our intellectual property portfolio in this space. In particular, our team was invited to give a platform talk [4] at the Eye and Chip Research Congresses (Detroit, US), which has a high impact in the field of visual neuroscience and implantable bionics. In addition, our team was invited to present our recent progress at the Feinstein Institute for Medical Research, NY, US [5]. Finally,

we organised a special session [6] on retinal neuroprosthetics at the 2019 International IEEE, Engineering in Medicine and Biology Conference, Berlin, Germany.

Building on and generalising beyond these studies, we have extended this research through new joint research projects with leading international universities through joint research projects with Harvard Medical School USA, University of Tübingen Germany, Shanghai Jiao Tong University China, Chinese Academy of Science China, These collaborations resulted in four successful research fund applications including:

●2020 UNSW-CAS Collaborative Research Bridging Grant.

●2020 UNSW-CAS Collaborative Research Mobility Grant

●2019 Australia-Germany Co-operation Scheme Fund

●2019 UNSW-SJTU Seed Fund.

This international funding is vitally important to maintain our advantage and foster existing international collaborations, amalgamate us with global efforts to satisfy urgent research demands in the field, promote the exchange of expertise, and increase value for money far beyond the outcomes of this project. Two Australian Research Council project grants have also been submitted to extend this work.

Reference (*The support of Retina Australia has been acknowledged in all publications of work funded wholly or in part by the grant*)

[1] “Towards Controlling Functionally-Distinct Retinal Ganglion Cells In Degenerate Retina”, by Madhuvanthi Muralidharan, Guo, Tianruo; Shivdasani, Mohit; Tsai, David; Fried, Shelley; Morven Cameron, John W. Morley, Socrates Dokos and Nigel H. Lovell, submitted to 2020 Annual International Conference of the IEEE, Engineering in Medicine and Biology Society (EMBS)

[2] “Neural activity of functionally different retinal ganglion cells can be robustly modulated by high-rate electrical pulse trains" by Madhuvanthi Muralidharan, Guo, Tianruo;Shivdasani, Mohit; Tsai, David; Fried, Shelley; Li, Liming; Dokos, Socrates; Morley, John; Lovell, Nigel. submitted to Journal of Neural Engineering, Special Issue on The Eye and the Chip

[3] “Creation of Virtual Channels in the Retina using Synchronous and Asynchronous Stimulation – A Modelling Study" by Song, Xiaoyu; Guo, Tianruo; Shivdasani, Mohit; Dokos, Socrates; Lovell, Nigel; Li, Xinxin; Qiu, Shirong; Li, Tong; Zheng, Shiwei; Li, Liming. submitted to Journal of Neural Engineering, Special Issue on The Eye and the Chip

[4] “Replicating a more physiological retinal neural code using high-rate electrical stimulation”, Eye and The Chip world research congress, November 2019, Detroit, US.

[5] “Australian Bionic Vision Story – From benchtop to clinical trials and beyond”, Feinstein Institute for Medical Research, November 2019, NY, US.

[6] “Selective Activation of Retinal Ganglion Cells, “ An invited session “Computational Models of Neuromodulation” under the theme “Computational Systems & Synthetic Biology; Multiscale Modeling” has been organised at the 2019 International IEEE Engineering in Medicine and Biology Conference (EMBC19) in Berlin, July 2019