The Retinal Implant Project

RLE Group
Retinal Implant Research Group

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Introduction to the Retinal Implant Project

The Retinal Implant Project is a joint effort of MIT, the Massachusetts Eye and Ear Infirmary, the VA Boston Healthcare System, the Cornell NanoScale Science & Technology Facility at Cornell University, and other collaborative branches to develop a retinal prosthesis to restore some vision to the blind. Diseases targeted include retinitis pigmentosa and age-related macular degeneration, both of which cause loss of the photoreceptors (rods and cones) of the outer retina, but spare the inner retinal ganglion nerve cells which form the optic nerve. As presently envisioned, a patient would wear a camera mounted on a pair of glasses, which transmits image data to an implant attached to the eye. The implant will electrically stimulate the appropriate ganglion cells via an array of microelectrodes. The concept is broadly analogous to a cochlear implant, but for vision rather than hearing.

For many years our group acted as a small research center for the interesting problems facing retinal prostheses. But in December 2002, we changed our direction, expanded our group, and decided to develop our own prototype for chronic implantation. This is a substantial effort, involving fabrication of flexible substrates and electrode arrays, circuit design, chip design and microfabrication, biocompatible and hermetic coatings, development of surgical procedures, and vendor development of RF coils and assembly processes. Our web site gives more information about the project and team: http://www.bostonretinalimplant.org/

Development of Second Generation Wireless Retinal Implants

Sponsors
NIH contract 1-RO1-EY016674-03
VA Center for Innovative Visual Rehabilitation
MOSIS provided IC fabrication at no cost

Project Staff
Bill Drohan, Patrick Doyle, Oscar Mendoza, Dr. Shawn Kelly, Professor John Wyatt

Over the past several years, we have developed a wireless retinal prosthesis prototype as the first step toward a human subretinal prosthesis. Last year, we were successful in implanting our first generation device in 3 animal models. This year, we focused on our second generation device, implanting active versions of the device in 2 animal models and refining our surgical technique and mechanical design over the course of multiple surgical trials.

Device Overview

Figure 1 shows the second generation prosthesis. Power and data are transferred wirelessly to the implant via RF fields from primary transmitter coils mounted in a pair of glasses. The secondary receiver coils are sutured around the iris. As with the first generation design, this approach avoids a cable connection between the eye and external hardware. The electrode array is placed in the subretinal space beneath the retina.

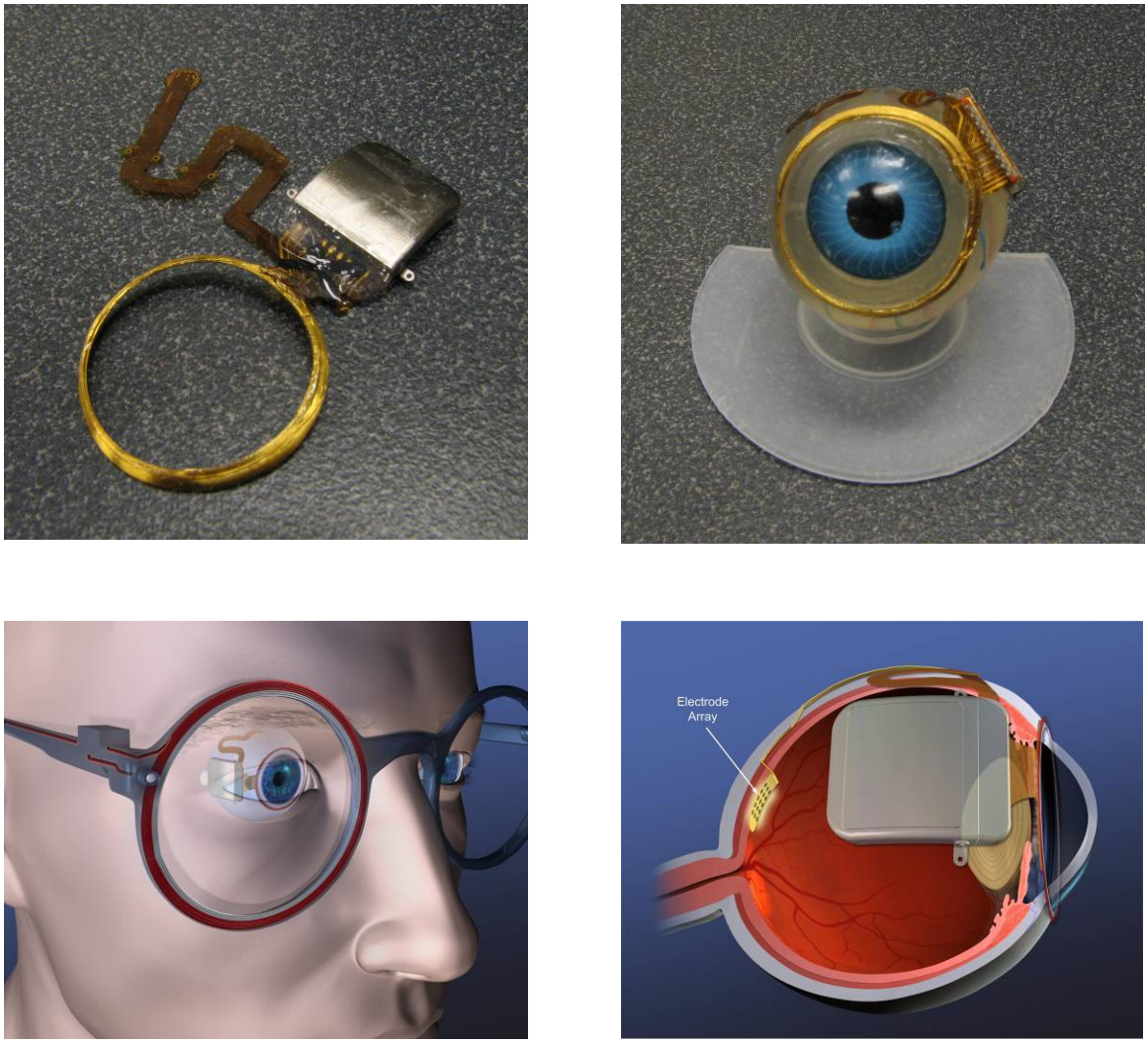

Figure 1. **Top:** Second-generation implant. All electronic parts are hermetically sealed in a titanium case with 19 feedthrough pins connected to an external flex circuit. The power and data coils are sutured to the eye around the iris (under the conjunctiva). **Bottom Left:** Artist's conception of the implant system. The image obtained by an external camera is translated into an electromagnetic signal transmitted wirelessly from the external primary data coil mounted on a pair of glasses to the implanted secondary data coil attached to the outside wall (sclera) of the eye surrounding the iris. Power is transmitted similarly. Most of the volume of the implant lies outside the eye, with only the electrode array penetrating the sclera. **Bottom Right:** The electrode array is placed beneath the retina through a scleral flap in the sterile region of the eye behind the conjunctiva.

Active Implant Surgical Trials

Previous issues of this report have documented the design and surgical trials of the first generation device. One of the most important changes from the first generation device was changing the placement of the secondary coil to be just beyond the circumference of the cornea. This change provides substantially more robust RF communication. The diameter of the coil that can be used in this location is much larger than that of the coil that was compatible with placement on the side of the eye (18 vs. 12 mm). Since received RF power increases as the cube of the diameter of the secondary coil, the anterior position for the secondary coil markedly increases the robustness of wireless communication.

In August of 2008, we implanted an active second generation device in a Yucatan minipig and demonstrated that it was functional following the surgery. In April of 2009, we repeated this surgery with a second device. An *ab externo* surgical technique was used in which the secondary coil was sutured around the cornea onto the anterior sclera while the electrode array was threaded under the superior rectus and inserted into the subretinal space. At the completion of the surgery, the whole implant was covered by the conjunctiva. No complications were observed during the surgeries, although both devices exhibited extrusion of the implant through the conjunctiva within a few weeks of the surgery. Following the surgery, we have demonstrated the correct operation of the device by placing a contact lens electrode on the surface of the cornea and measuring stimulus artifacts generated by the device upon command from the external controller.

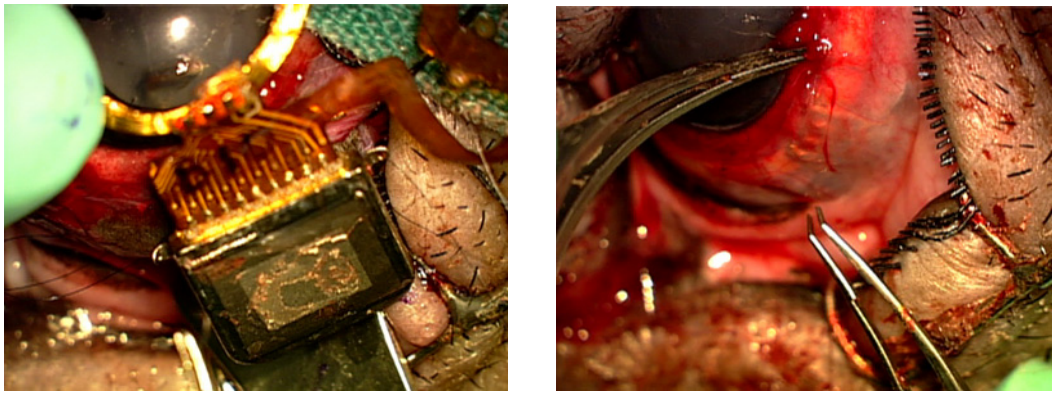

Figure 2. Photographs taken during and following the surgery**.**

Left: Suturing the implant to the sclera. **Right:** View prior to covering the device with the conjunctiva.

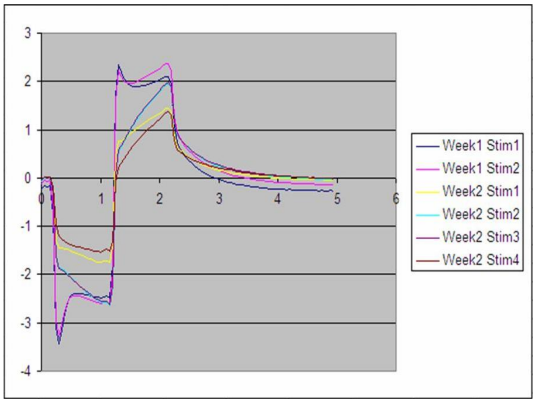

Figure 3 Stimulation artifact waveforms collected at weeks 1 and 2 following the surgery.

Electronics

The core of the first and second generation retinal prosthesis is a 25,000 transistor stimulator chip designed by Luke Theogarajan in 2005 and modified by Shawn Kelly in 2007. The chips were fabricated at no expense to the project thanks to the generosity of MOSIS. They produce variable current pulse durations, amplitudes, inter-pulse intervals and selections of the set of electrodes to be stimulated. These first versions of the chip worked well enough to be used in prototypes and in early animal experiments, but over the past three years we have discovered a number of changes and improvements that are necessary. The most urgent problem is that the signal transmission is not robust enough for chronic human trials. We also need to add a low-bandwidth back-telemetry channel to enable us to monitor electrode voltages and impedances.

This past year, two new designs were developed in conjunction with a commercial partner, Sigenics, Inc. under the direction of Dr. Philip Troyk, PhD. The first design marries an existing neurostimulator IC to an existing low power bidirectional wireless communications IC. This design features a more robust communication link (using FSK instead of ASK) and provides the back-telemetry capability required to monitor the health of the device and characteristics of the tissue surrounding the electrode array. It does not, however, provide the safety features and other capabilities required for human trials. Consequently, we have started the process of developing the specifications for a custom device that would meet those requirements.

Hermetic Package and Feedthroughs

In previous issues of this report, we have described the problems associated with the hermetic packaging for the first generation device. To combat those problems, we developed the state-of-the-art hermetic micro-package shown above. Our overarching objective has been to develop a packaging approach that will eventually be scalable to 100s of I/O channels in the future. Given the fact that the current state of the art in implantable neurostimulator packaging involves enclosures with approximately 20 feedthroughs (e.g., our current device), one might expect that this technology might not scale up to the future needs of retinal prosthetics. One surprising result that emerged from our research in the past three years, however, is that the pitch between output channels in our current implant (500 microns) may actually be maintained when a larger ceramic substrate is used and 100+ pins are placed through it. Figure 4 shows a conceptual sketch of a 104-pin feedthrough with all the channels contained within a ceramic disc 7 mm in diameter.

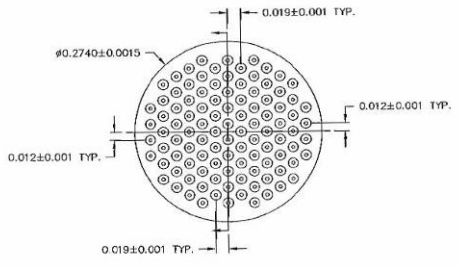

Figure 4. Proposed 100+ ceramic feedthrough w/500 micron pitch, to be incorporated into the lid of a Ti case similar in size to that shown previously. The stimulator IC would be located immediately adjacent to this feedthrough assembly on the inside of the case.

This disc would form part of the lid of a Ti enclosure with geometry similar to that shown in Figure 1. The connection to the external flexible circuit would be made by laying that circuit over the external side of the enclosure and making the connections with screen-printed, gold-loaded biocompatible conductive epoxy. By utilizing two rectangular ceramic sections containing 75 feedthroughs each, it is conceivable that even 150 I/O channels may be achievable within a Ti enclosure approximately the same size as that we are currently implanting. We plan to continue developing a 150 – 200 feedthrough hermetic case using this approach.

Surgical Technique Results and Refinements

First Generation Device

We completed our first generation *in vivo* experiments this past year. The longest term experiment lasted 10 months. Figure 5 shows the results of conventional histology and immunohistochemistry following explantation of the device. The retina looks quite normal.

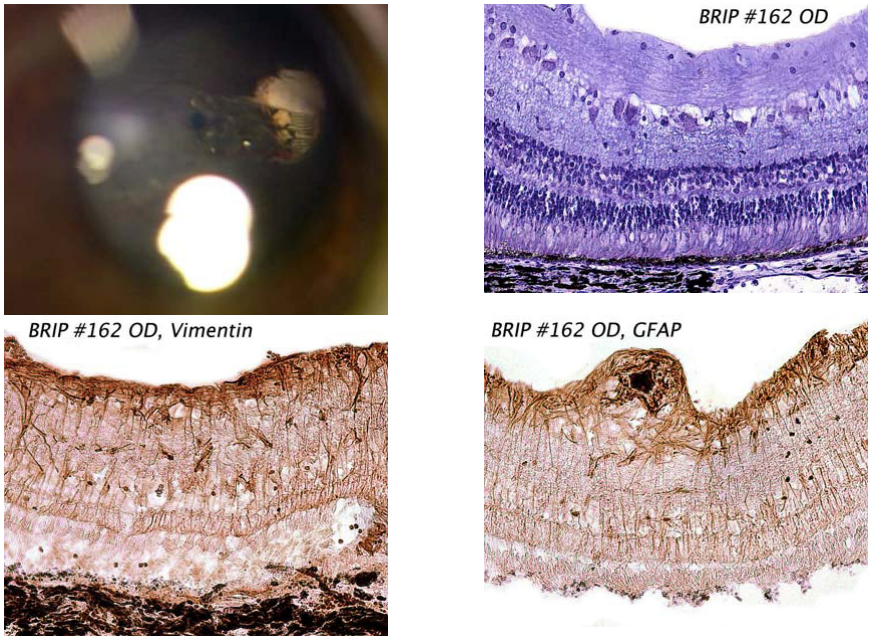

Figure 5: Results from long term first generation implant experiment.
Top Left: Fundus photograph showing the array inserted in the subretinal space.
Top Right: Standard histology.
Bottom Left: Immunohistochemistry slice stained with anti-Vimentin.
Bottom Right: Immunohistochemistry slice stained with anti-GFAP.

Surgical Refinements

Unfortunately, our two surgeries with our second generation device resulted in exposure problems of the device. Within the first few weeks following the surgery, the conjunctiva either failed to heal, or eroded away where it was sutured over the device. Consequently, most of our surgical effort focused on modifying the design and refining our surgical techniques for implanting the device. We made the coil flatter and we moved the periotomy to be more posterior. We performed three surgeries of mockup (i.e. inactive) devices with little to no complications or device exposure following the surgery.

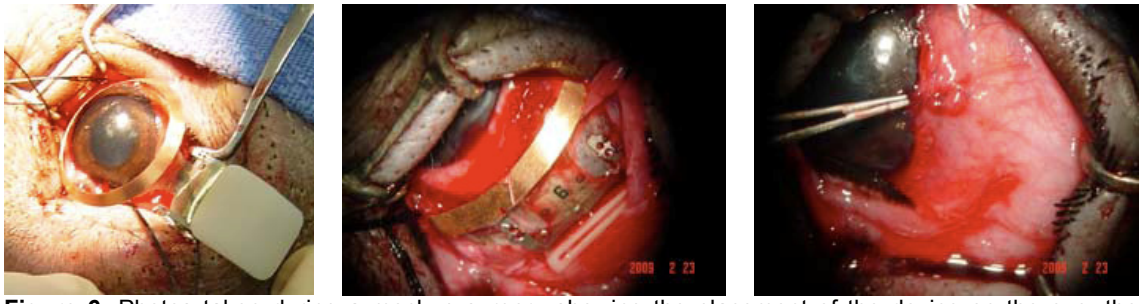

Figure 6: Photos taken during a mockup surgery showing the placement of the device on the eye, the placement prior to closing the conjunctiva, and the results at the end of the surgery.

Penetrating Electrode Arrays

Electrodes that penetrate the retina will greatly shorten the distance between electrodes and retinal ganglion cells and should thereby lower stimulation thresholds. They can also cause a reduced area of stimulation for each electrode, resulting in more detailed image perception.

This past year we successfully implanted four penetrating electrode arrays into Yucatan minipig eyes. In conjunction with the *Cornell NanoScale Science & Technology Facility* (CNF), we constructed pillar arrays consisting of a flexible polyimide base with 112 μm-tall, 30 μm diameter SU8 pillars on a 13 μm thick, 1.7mm × 15mm, flexible polyimide base. An *ab externo* surgical method was used to implant these arrays into the subretinal space with no complications observed during the surgery. Optical coherence tomography (OCT) showed good contact between the array and the retina. Histology showed that the pillars were integrated into the inner nuclear layer.

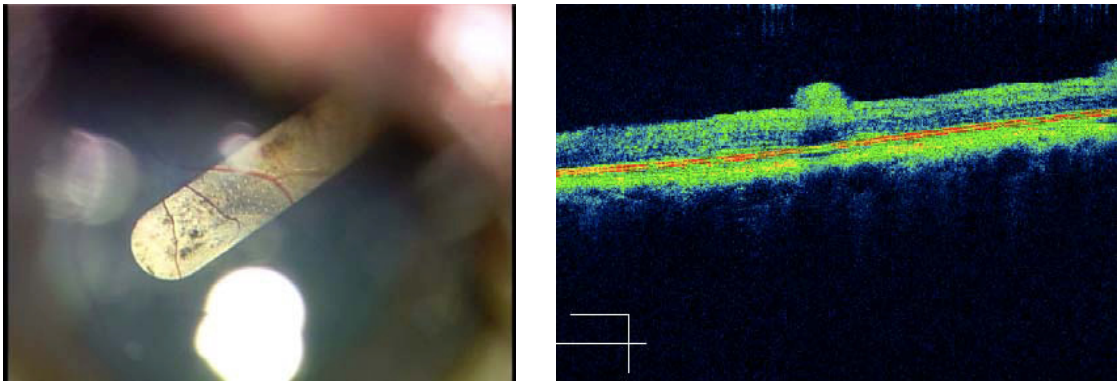

Figure 7: Left: Fundus image of pillar array inserted in subretinal space. **Right:** OCT image of the array.

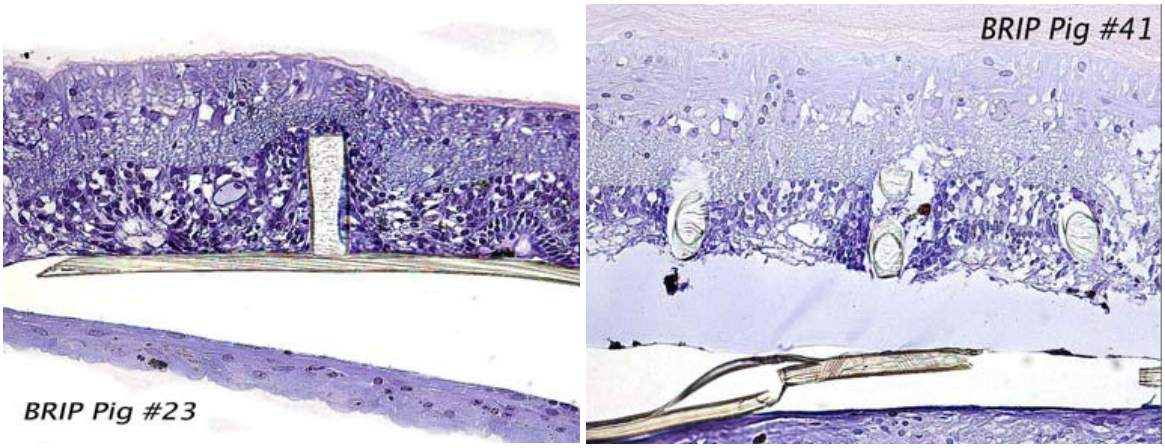

Figure 8: Standard histology of the retina three months after implantation of second prototype pillar array.

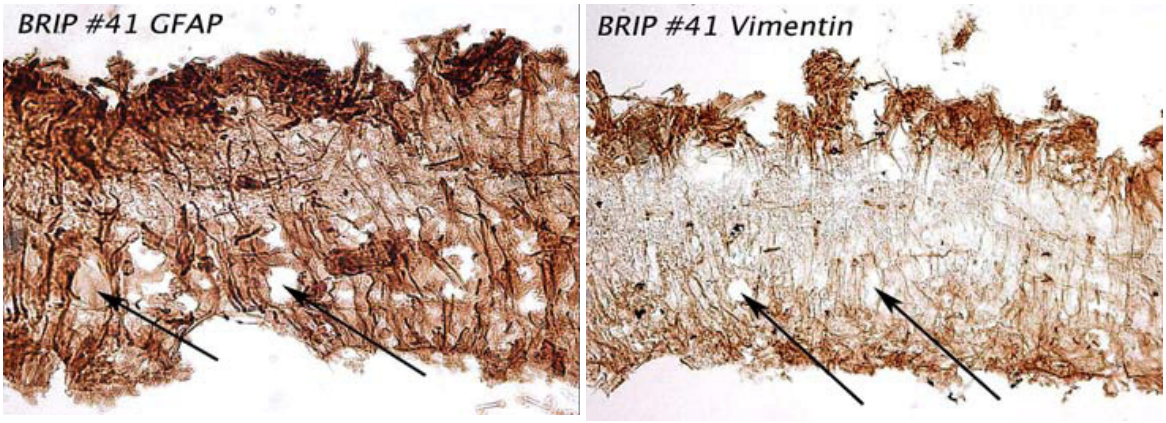

Figure 9: Immunohistochemistry (stained with anti-GFAP and anti-Vimentin.) Arrows show possible spaces formerly occupied by pillars.

Inferring Visual Input from Retinal Ganglion Cells

Sponsors
National Science Foundation: NSF No. IIS-0515134, NSF Graduate Research Fellowship

Project Staff
Yi-Chieh Wu, Dr. Ofer Ziv, Prof. John Wyatt

Introduction

The neural system represents and transmits information through a complicated network of cells and interconnections. A major challenge in neuroscience is understanding how this encoding and decoding takes place. For the retinal implant, such an understanding can provide an objectively measurable metric for comparing the responses to electrical and optical stimulation of retina.

The purpose of this work is to understand what information is available at the retinal ganglion cell (RGC) layer in the hopes of developing a model for neural representation that can be used in a retinal implant. In this particular project we project light patterns on retinal sections while recording from a microelectrode array. We first model the optical response behavior of each cell separately, and then use the combined responses of all the cells to reconstruct the original image or moving light pattern from the ganglion cell outputs. This approach gives a quantitative measure to our interpretation of the ganglion cell firing patterns.

Method

Using the responses from a collection of ON and OFF RGCs simultaneously recorded from a microelectrode array (MEA), we estimate the speed and direction of a moving edge of light (see Figure 10). We develop a neural model based on physiological characteristics, with model parameters fitted by maximizing a cost function (the likelihood) over a training set of spike responses. We then use neural responses from new visual stimuli to estimate the stimulus parameters.

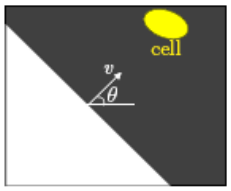

Figure 10: Moving edge stimulus. For an ON stimulus, a bright bar of constant intensity moves at a constant speed v and in a constant direction θ. An OFF stimulus is identical except the bright and dark pixels are interchanged.

Neural Model

To characterize neural behavior, we use a Poisson model. A simple interpretation of this model is that the stimulus is linearly filtered by the neuron's spatiotemporal receptive field to produce an intracellular voltage (also known as a generator signal). The voltage is converted via a memoryless nonlinearity to an instantaneous spike rate, and this rate yields a set of spikes via an inhomogeneous Poisson process.

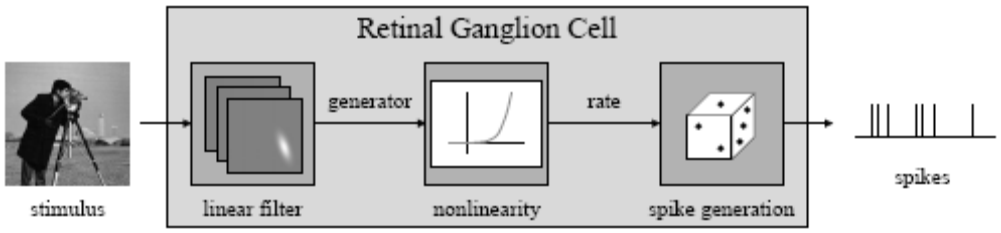

Figure 11: Linear-nonlinear Poisson model. The LNP model depicts how a visual stimulus is transformed by the retina into a spike response. The model consists of a linear filter followed by a point nonlinearity followed by Poisson spike generation.

For simplicity, we have assumed the spatiotemporal receptive field (RF) to be *separable,* i.e., the spatial filtering is done first to produce a time signal which is linearly filtered. Then the time-varying firing rate $\lambda(t)$ of a cell is given by

$$\lambda(t) = n\left(\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(x,y)\,s(x,y,t) * h(t)\right)$$

where $f(x, y)$ specifies the spatial sensitivity function, $h(t)$ specifies the temporal sensitivity function, $s(x, y, t)$ specifies the stimulus, $n(\cdot)$ specifies an arbitrary point nonlinearity, and $*$ specifies convolution in time. The idea is simple: if $h(t)$ denotes the response to a single pixel flash, we multiply the spatial response $f(x,y)$ by the light intensity $s(x,y,t)$, convolve the result with the temporal response function $h(t)$, and substitute into the nonlinearity.

To fit the model to the actual ganglion cell response, we use maximum likelihood (ML) methods that treat the spike times as an inhomogeneous Poisson process. We find the model parameters for each cell that maximize the likelihood of the observed response for that cell, given the (known) experimental stimulus. Then, we use the combined responses of all the cells to estimate the parameters of a new stimulus. The *maximum likelihood estimate* we use is the estimate that maximizes the likelihood of the observed spike response, given the model parameters estimated as described above.

Results

Data was obtained through collaboration with Dr. Steven F. Stasheff in the Department of Pediatric Neurology and Neuro-opthalmology at the University of Iowa, and Dr. Ofer Ziv in the Research Laboratory for Electronics at the Massachusetts Institute of Technology.
They both visually stimulated rabbit retina and recorded in-vitro responses using a 60-channel multi-electrode array (MEA). Data from four rabbit retina were collected for stimulation with moving edges.

Figure 12 shows that the method gives a reasonably accurate characterization of the response of some cells to a moving-edge stimulus. Figure 13 shows the likelihood function for the low-dimension parameter space of a moving edge. Note that while the landscape may not be convex, there is a well-defined global maximum that corresponds to the ML estimate of the visual stimulus parameters.

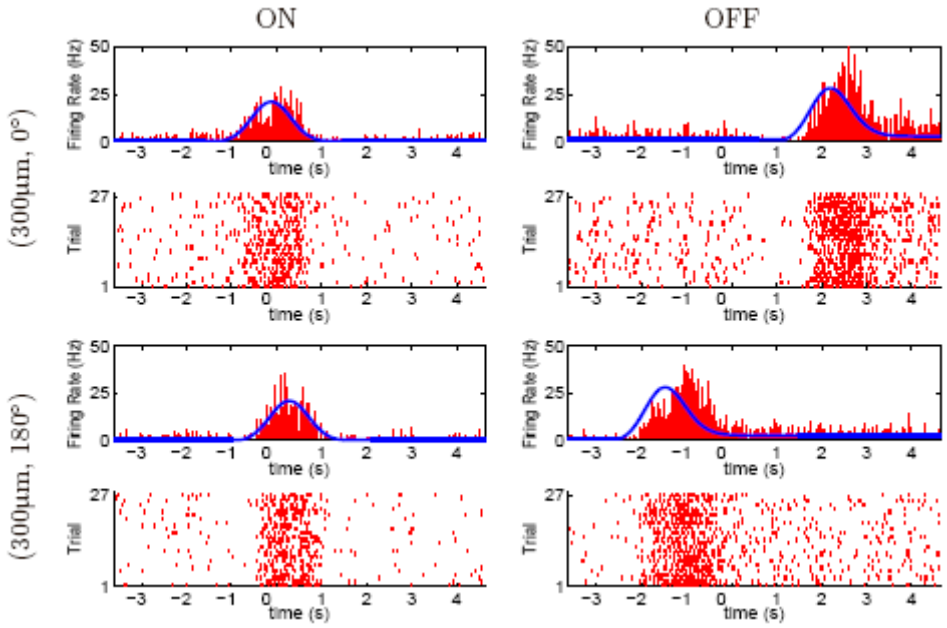

Figure 12: Estimated versus expected firing rates. PSTH and raster plots over 27 trials for the ON RGC and OFF RGC. From *top* to *bottom*, the stimulus was an edge of matching polarity moving at 300 µm/s in the (0°, 180°) direction. The model was fit using the data from 48 runs (3 trials, 1 polarity, 4 speeds, 4 directions). The blue line in the PSTH plot indicates the expected firing rate as estimated by the model.

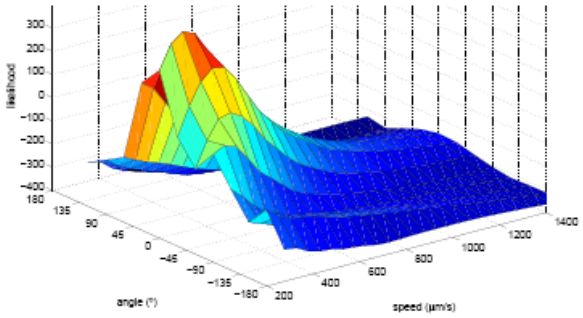

Figure 13: Likelihood landscape. The likelihood of (ON, v, θ) stimuli obtained from the responses of the ON cells of one retina in one trial. The ML estimate was found at (305.1 µm/s, 1.7°), compared to the true stimulus of (300 µm/s, 0°).

Publications

Journal Articles

D.B. Shire, S.K. Kelly, J. Chen, P. Doyle, M.D. Gingerich, S.F. Cogan, W. Drohan, O. Mendoza, L. Theogarajan, J.L. Wyatt, and J.F. Rizzo, “Development and Implantation of a Minimally-Invasive Wireless Sub-Retinal Neurostimulator”, accepted for publication in IEEE Trans. on Biomedical Engineering, 2009

Talks and Posters Presented

S.K. Kelly, "Functional Vision for the Blind: The Boston Retinal Implant." Boston Chapter of the IEEE Society on Social Implications of Technology, September 2008

W. Drohan, S.K. Kelly, J.F. Rizzo, and J.L. Wyatt, “Electrode and Axon Models” Poster 4574 at The Association for Research in Vision and Ophthalmology (ARVO), May 2009.

S.K. Kelly, P. Doyle, O. Mendoza, G.W. Swider, D.B. Shire, J.L. Wyatt, and J.F. Rizzo, “Improved Class A Based Transmitter System for Wireless Retinal Implant Data Telemetry” Poster 4578 at The Association for Research in Vision and Ophthalmology (ARVO), May 2009.

M.D. Gingerich, R.A. Akhmechet, O. Ziv, D.B. Shire, J.L. Wyatt, and J.F. Rizzo, “Microfabricated Multi-Electrode Arrays for in vitro Studying Neural Coding in the Retina” Poster 4587 at The Association for Research in Vision and Ophthalmology (ARVO), May 2009.

P. Doyle, S.K. Kelly, O. Mendoza, W. Drohan, D.B. Shire, J.L. Wyatt, and J.F. Rizzo, “A System for Developing Feature Extraction Algorithms for Retinal Implant Devices” Poster 4591 at The Association for Research in Vision and Ophthalmology (ARVO), May 2009.

D.B. Shire, S.K. Kelly, M.D. Gingerich, O. Mendoza, W. Drohan, J. Chen, J.F. Rizzo, and J.L. Wyatt, “Long-Term in-vivo Operation of the Wireless Boston Retinal Neuroprosthesis” Poster 4596 at The Association for Research in Vision and Ophthalmology (ARVO), May 2009.

Theses

Yi-Chieh Wu, “Deciphering the Neural Code for Retinal Ganglion Cells through Statistical Inference.” M.S. thesis, Dept. of EECS, MIT, June 2009.