The Retinal Implant Project

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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: www.BostonRetinalImplant.org.

Development of First and 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, Greg Swider, Patrick Doyle, Oscar Mendoza, Dr. Ofer Ziv, 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. This past year, we were successful in implanting our first generation device in 3 animal models. At the time this report was prepared, the earliest implanted device had been operating wirelessly in an animal for over 4 months

Active Implant Surgical Trials

In March of 2008, we implanted an active first generation device (shown in Figure 1) in a Yucatan minipig and demonstrated that it was functional following the surgery. In May, we successfully repeated this surgery twice more. An *ab externo* surgical technique was used in which the secondary coil was sutured temporarily onto the superior sclera while a 7 mm long, 1.5 mm wide, 15 μm thick polyimide array was 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 some extrusion of the implant through the conjunctiva was later observed.

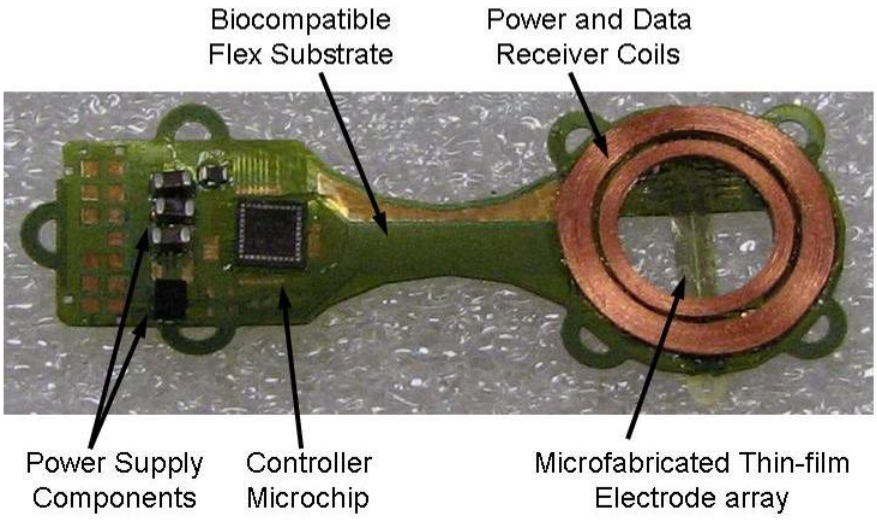

Figure 1. Detailed mockup of the first-generation implant. All parts are mounted on a 25-um thick flexible substrate, which has conducting wires embedded within. The thin neck is placed beneath the superior rectus muscle during implantation. The implant is sutured to the sclera through the seven semicircular tie points shown.

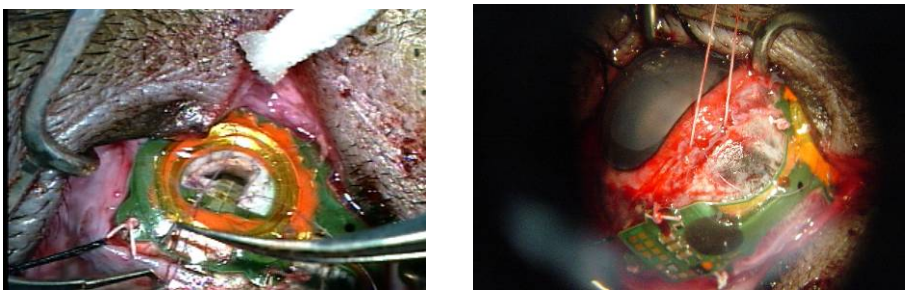

Figure 2 Photographs taken during surgery.

Left: Suturing the implant to the sclera.

Right: View prior to covering the device with the conjunctiva.

We have operated the device wirelessly and captured stimulation artifact waveforms via a contact lens electrode placed on the eye of the animal, demonstrating the operation of the device. In the 3 months since the first surgery, we have continued to refine and optimize the control circuitry and the sense circuitry.

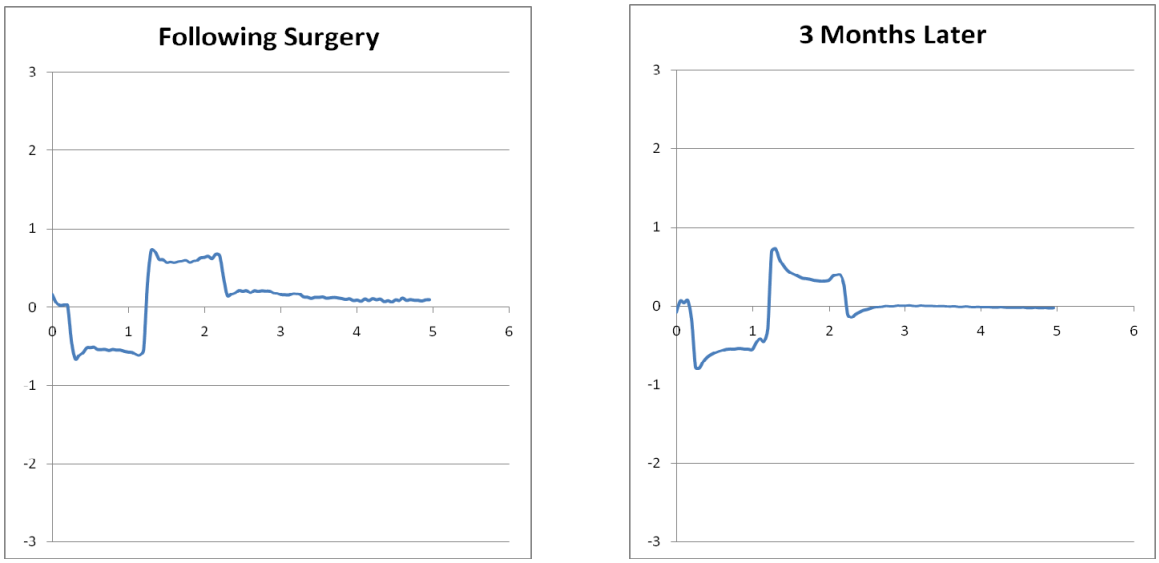

Figure 3 Stimulation artifact waveforms collected immediately following the surgery and 3 months later.

Second Generation Implant Design

Figure 4 shows an artist's conception of the second generation prosthesis. Power and data are transferred wirelessly to the implant via radiofrequency (RF) fields from the primary transmitter coils mounted in a pair of glasses to the secondary receiver coils sutured around the iris. As with the first generation design, this approach avoids a cable connection between the eye and external hardware, and the electrode array is placed in the subretinal space beneath the retina. A mockup is shown in Figure 5.

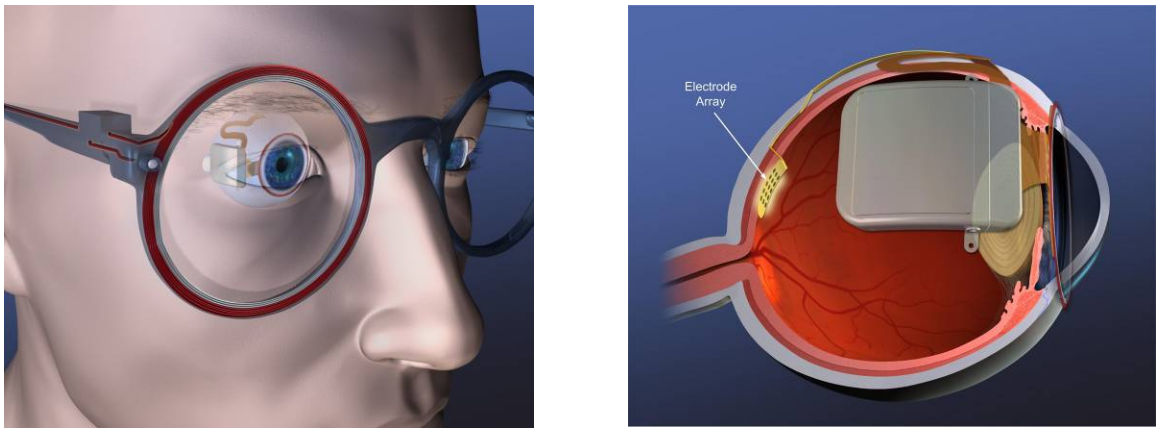

Figure 4. **Left:** Artist's conception of the second generation implant system. The image obtained by an external camera is translated into an electromagnetic signal transmitted wirelessly from the external primary data coil mounted on a pair of glasses to the implanted secondary data coil attached 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. **Right:** The electrode array is placed beneath the retina through a scleral flap in the sterile region of the eye behind the conjunctiva.

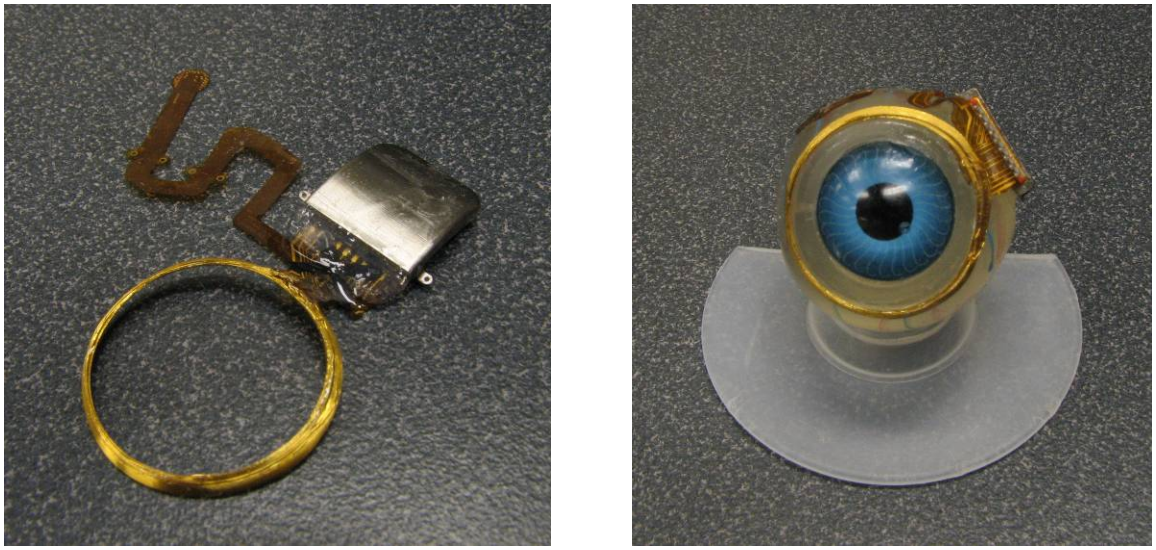

Figure 5. Mockup of the second-generation implant. All electronic parts are hermetically sealed in a titanium case with 19 feedthrough pins connected to an external flex circuit. The power and data coils are sutured to the eye around the iris (under the conjunctiva) while the electrode array is inserted subretinally at the back of the eye. The case is sutured to the sclera through the two suture tabs shown.

Electronics

The core of the retinal prosthesis is the 25,000 transistor stimulator chip. Two versions currently exist and two more are under development. The original device was designed by Luke Theogarajan in 2005. This design was modified by Shawn Kelly in 2007 to reduce the power consumption at reset and to provide additional visibility into the internals of the device. Both versions were fabricated at no expense to the project thanks to the generosity of MOSIS. The chips 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 two 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.

Two new designs are in development currently. The first design marries an existing neurostimulator IC to an existing low power bidirectional wireless communications IC, both of which are available from a commercial partner, Sigenics. This design will feature a more robust communication link (using FSK instead of ASK) and will provide the back-telemetry capability required to monitor the health of the device and characteristics of the tissue surrounding the electrode array. It will not, however, provide the safety features and other capabilities required for human trials. Consequently, we have started the process of designing a custom device (in conjunction with Sigenics) that meets these requirements.

Hermetic Package and Feedthroughs

Our first generation wirelessly driven implant (currently in animal models) was designed to be encapsulated in parylene-C for saline testing and animal implantation. However, soak tests revealed minor delamination of the parylene coating, as well as corrosion of the exposed metal

current return region. Consequently, this encapsulation method is not suitable for long-term animal studies (months or years) or for the clinical human studies that will eventually be required.

Two years ago, we commenced development of new state-of-the-art hermetic micro-package technology for our retinal prostheses devices. Our efforts focused on the design and construction of the hermetically sealed microelectronics package for our existing wirelessly powered retinal prosthesis device. By using the existing electronics design, we will have a proven electronics platform available to evaluate the performance of the new hermetic packaging. Our initial hermetic package design provides for an internal electronics flex to connect to a ceramic hermetic feedthrough. This allows the electrode drive wires, as well as the power and data coil wires, to pass through the packaging without leakage. The hermetic package will allow us to proceed to longer term animal surgical trials with a 15 electrode implant. This past year we have refined the design to the anterior coil based configuration shown in Figures 4 and 5. We anticipate surgical trials of hermetically sealed active implants in the second half of 2008.

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 two 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 6 shows a conceptual sketch of a 104-pin feedthrough with all the channels contained within a ceramic disc 7 mm in diameter.

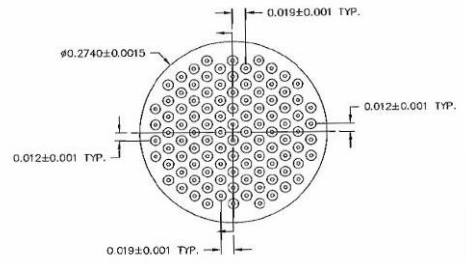

Figure 6. Proposed 100+ ceramic feedthrough w/500 micron pitch, to be incorporated into the lid of a Ti case similar in size to that shown in Figs. 4 and 5. The stimulator IC would be located immediately adjacent to this feedthrough assembly on the inside of the case.

This disc will form part of the lid of a Ti enclosure with geometry similar to that shown in Figure 5. The connection to the external flexible circuit will 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 this approach.

Surgical Technique Refinement

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.

We successfully implanted three penetrating electrode arrays into Yucatan minipig eyes. (See Figure 7). In conjunction with the *Cornell NanoScale Science & Technology Facility* (CNF), we constructed pillar arrays consisting of a flexible polyimide base with 70 μm-tall, SU8 pillars of various diameters ranging from 10 - 80 microns. An *ab externo* surgical method was used to implant these arrays into the subretinal space with no complications observed during the surgery. These pigs were followed for three months before histology tests were performed. On the histology slides we can see that the pillar electrodes were integrated into outer nuclear layers. (See Figure 8).

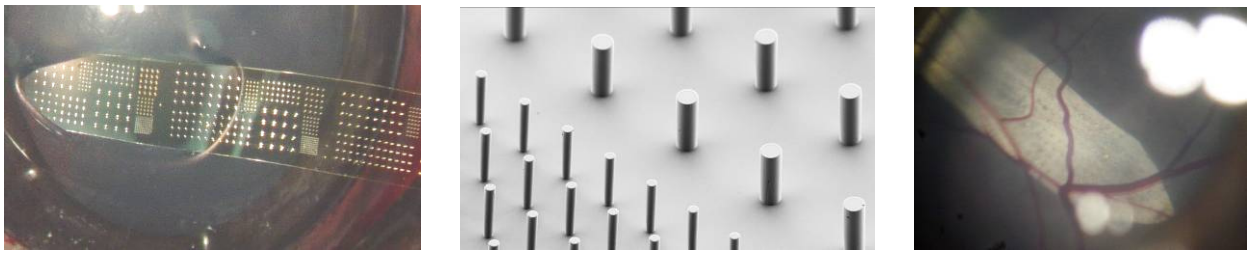

Figure 7.

Left: Penetrating electrode array. **Center:** SEM image of the 70 μm tall SU8 pillars. **Right:** Fundus photo of implanted array.

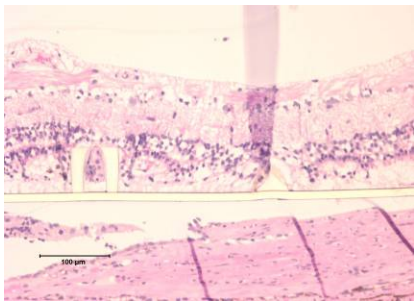

Figure 8 Histology slide showing integration of penetrating electrode with the outer nuclear layers.

Multiple Array Implantation
To improve the ability of severely blind patients to walk safely in unfamiliar environments, we performed surgeries to implant two arrays into one eye. A large array was located in the periphery to stimulate larger area of retina. This array would be more useful for navigation. A smaller array was located more centrally. Potentially, this array would be more useful for visual tasks that require higher spatial resolution. We implanted 4 pairs of arrays into 4 minipig eyes using an *ab externo* approach. Three out of four surgeries were successful. See Figure 9. No other group has ever attempted this type of surgery.

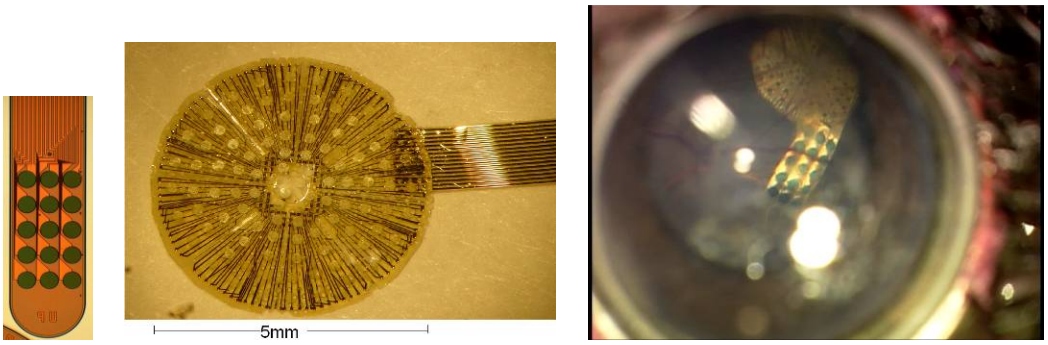

Figure 9: Large and small electode arrays. **Left:** 1.5mm wide array would allow 4.1 ° of visual angle when inserted behind the central portion of the retina. **Center:** 5mm diameter array would allow a much larger field of view, 13.75 ° of visual angle, when inserted behind the periphery of the retina. **Right:** Fundus picture of large array.

Deciphering the Retinal Neural Code for Motion

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

Project Staff
Yi-Chieh Wu, Shamim Nemati, Stavros Valavanis, Prof. John Wyatt

Introduction

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

Towards this end, we are developing algorithms for a visual decoder using the responses from a population of retinal ganglion cells (RGCs). We stimulate rabbit retina with a visual stimulus, record responses using a multi-electrode array, and attempt to reconstruct the scene. In this first phase, we focus on a small subset of cell types known as ON, OFF, ON/OFF cells and analyze the encoding of global motion using relatively simple artificial movies characterized by a small set of parameters. The movie consists of a wide bar moving across the retina at various speeds and angles, with the accuracy of our algorithm determined by looking at the errors in speed and angle estimation.

Method

We use a statistical framework based on receptive field models and likelihood methods. To characterize neural behavior, we use the popular 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.

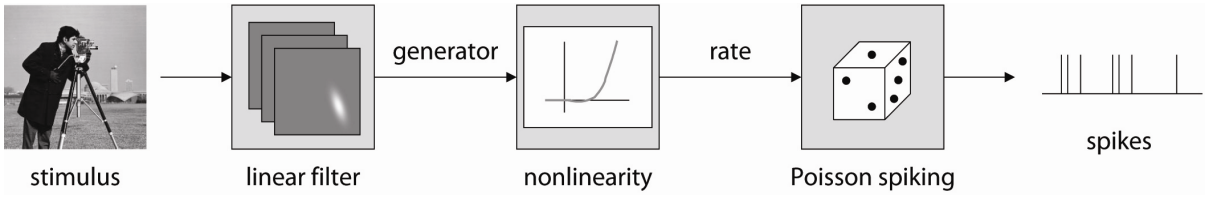

Figure 10. Linear-nonlinear Poisson model consisting of a linear filter followed by a point nonlinearity followed by Poisson spike generation.

For simplicity, we have assumed the spatiotemporal receptive field (RF) to be separable and used a simple maximum function for the nonlinearity. Then the time-varying firing rate $\lambda(t)$ of a cell is given by

$$\lambda(t) = \max\left\{\int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f(x,y)\,I(x,y,t)\,dx\,dy * h(t), c\right\}$$

where *f*(*x*, *y*) represents the spatial sensitivity function, *h*(*t*) represents the temporal sensitivity function, *I(x, y, t)* represents the image intensity, *c* represents minimum background firing rate, and the * symbol represents 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 *I(x,y,t)*, convolve the result with the temporal response function *h(t)*, and substitute into the nonlinearity. For simplicity, we have chosen analytically tractable functions for *f*(*x*, y*)* and *h(t*) that have a basis in physiology and are supported by experimental recordings: *f*(*x*, *y*) is a single possibly elliptical Gaussian, and *h*(*t*) is a delayed decaying exponential.

Under the assumption of Poisson spiking, the probability of a spikes occurring at specific times follows a simple equation, and if we further assume that the cells act independently, we can use maximum likelihood to determine the most likely stimulus corresponding to a given set of responses.

This procedure was separated into a training phase in which we knew the visual stimulus and examined the RGC outputs to determine the cell model parameters, and a testing phase in which we examined RGC outputs elicited by moving edges with unknown speeds and directions. In both cases, the unknown parameters (either for the model or for the stimulus) were chosen to maximize the joint likelihood of the observed responses.

Results

After manually identifying 5 ON cells, 7 OFF cells, and 1 ON-OFF cells, we trained using 256 stimuli and found that the RF locations closely match those of the electrodes from which they were recorded (Fig. 11) and that estimated and experimental firing rates closely match (Fig 12).

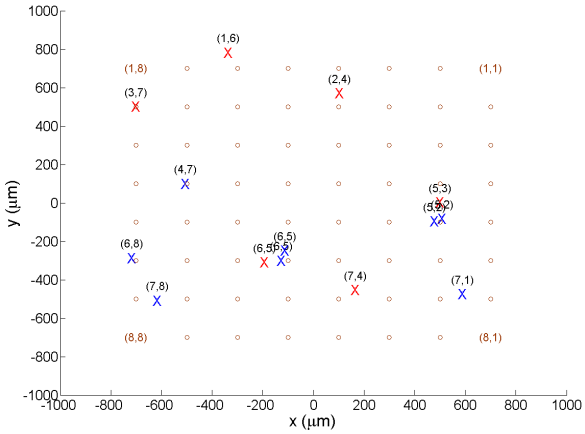

Figure 11. Spatial receptive field locations estimated by the maximum likelihood algorithm for ON cells (red X) and OFF cells (blue X). Cells are labeled by the electrode from which their response was recorded. The regularly spaced brown circles show the location of the electrodes on the microelectrode array for comparison to the cell locations. The four corner electrodes are labelled (1,1), (1,8), etc to explain the electrode numbering system.

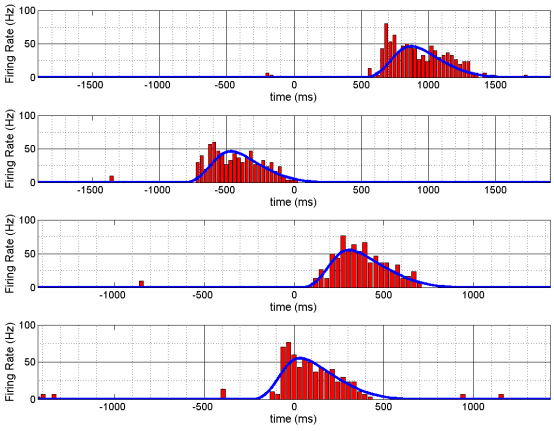

Figure 12. PSTH plots (red) show the spike firing pattern vs. time for a given stimulus over 10 trials for the OFF cell recorded from electrode (5, 2). The stimuli move at a speed of 714 µm/s to the right, left, up and down in the four figures, beginning from the top plot. The blue line in the PSTH plot represents the firing rate profile estimated by our model.

In the testing phase, we experimented with decoding multiple speeds and directions and found that the typical likelihood landscape is smooth with a single maximum (Fig. 13). We also observed the following results from the estimations:

1. modest numbers of ON or OFF RGCs send quite accurate information on global motion to the brain,
2. estimates for speed are better at lower speeds, with less tendency towards overestimation,
3. estimates for direction are comparable regardless of true speed,
4. no direction is preferred over another,
5. estimates for direction are better (less bias, lower spread) than those for speed,
6. estimate spread decreases and fewer outliers exist as the number of cells increase and as the spacing across cells increase.

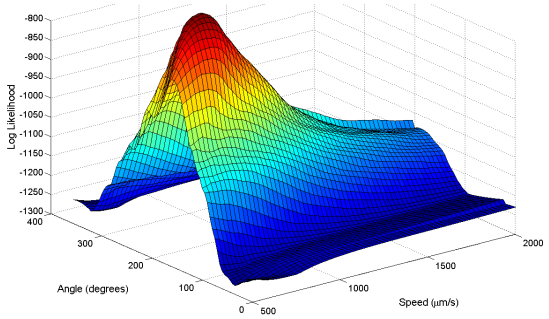

Figure 13. Likelihood landscape for an OFF stimulus of (714 μm/s, 180°) using all 7 off-cells. The log-likelihood is plotted as a function of possible angles and speeds for the moving edge. The maximum was found at the *maximum likelihood estimate*, a value of (728.7 μm/s, 182.6°).

Conclusions and Future Work

We have presented an algorithm to interpret how ganglion cell firing patterns represent visual input. We found that moderate estimation accuracy is possible using the responses of only 3-5 cells. Furthermore, this method allows for the characterization of other cell types (e.g., directionally selective cells) and arbitrary stimuli, and we are looking to refine the algorithm using better approximations for the temporal response function and alternative stochastic models. So far, we have only considered a particularly simple form of the decoding problem (a moving edge), and we will next attempt to reconstruct stimuli that cannot be characterized by a simple set of parameters. The class of natural images is of particular interest, and a long term goal is to understand how they are represented in the RGC neural code.

Retinal Recording System

Sponsor
National Science Foundation: NSF No. IIS-0515134

Project Staff
Dan Kumar, Prof. Rahul Sarpeshkar, Professor John Wyatt

This hardware project aims to develop an ultra-low-power recording system that can be implanted adjacent to the retina of a freely moving animal with normal or impaired vision. It will wirelessly transmit recorded retinal ganglion cell action potentials to an outside receiver. This will enable experimentalists for the first time to relate retinal firing patterns to the behavior of an awake, mobile animal. This device will eventually enable researchers to study the retinal firing patterns of healthy and diseased retina in behaving animals in order to design a more useful retinal implant for the blind.

This work is carried out in the laboratory of Prof. Rahul Sarpeshkar under the direction of Profs. Sarpeshkar and Wyatt.

The block-diagram of the retinal recording system is illustrated in Fig.14 below. Neural activity picked up by a high-impedance electrode will be amplified with an ultra-low-power neural amplifier before being digitized. The digitized neural signals will then be compressed using the digital interface subsystem to reduce the data rate before being wirelessly transmitted via a bi-directional wireless link to an external device for analysis.

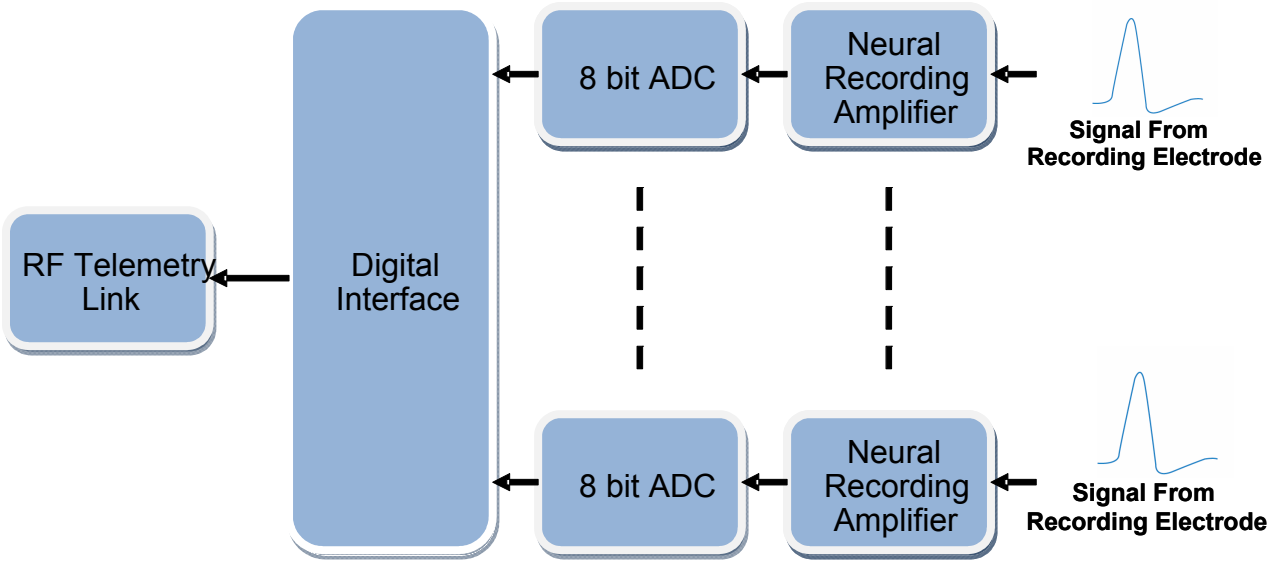

Figure 14: Block Diagram of the Retinal Recording System

Progress

To date, the following sections in this system have been designed:

- **Low-noise, low-power neural amplifier:** An initial version of the neural amplifier was designed and fabricated using the 0.5 µm AMI process. This amplifier has been tested and was shown to operate very robustly. Furthermore, the amplifier appears to be the most power-efficient neural recording amplifier in the literature to date. An improved version of this front-end amplifier, which is suitable for a multi-electrode system due to its small area, has been designed in the 0.18 µm TSMC process and is currently being fabricated at no cost to this grant (thanks to the donation of fabrication from MOSIS).

- **Low Power Analog-to-Digital Converter (ADC):** An initial version of the Low Power ADC has been designed in the 0.5 µm AMI process. An improved version of this design, implemented in the 0.18 µm process, will be sent out for fabrication in August, 2008.

- **Digital Interface:** An initial version of the digital interface with minimal programmability for a small number of recording channels was designed and fabricated using the 0.5 µm AMI process. An extended version of the digital interface that includes programmability and data reduction ability will be sent out for fabrication in August, 2008.

Remaining Challenges

1. System integration

While some of the individual pieces have been fabricated and tested, integration of the entire system will pose some challenges. Integration of the low-noise analog systems with the digital circuitry will need to be done with great care to ensure enough electrical isolation between the tiny analog signals and the large switching noise from the digital circuitry.

2. Physical design of the implantable circuitry

The physical design of the implantable circuitry may pose further challenges on the system design. Surgical constraints with respect to the size of the incision that can be performed will dictate some physical characteristics of the system. This may be particularly challenging for the design of the wireless telemetry system that utilizes an implanted, off-chip inductive coil. The complexity of surgical procedures may limit the size of this coil, which will require careful engineering of the wireless telemetry system, particularly on the implanted side.

Final Product and Approximate Timeline

We expect the remainder of the development of the Retinal Recording System to undergo two major phases. In the first phase, we will focus on circuit design and optimization to achieve the optimal performances. At the end of the first phase, we expect to have a tested and functioning system (integrated at a printed-circuit-board level) that can be used on a lab bench. In the second phase, we will work on making the entire system implantable by integrating various subsystems in a single silicon die. At the end of this phase, we expect to have a functioning system that can be implanted into an animal model. The final product will have between 64 and 100 recording channels. A timeline of our expected progress is listed in Table 1 below.

Date	Goal Description
August, 2008	• First version of the integrated Retinal Recording System sent out to be fabricated.
November, 2008	• First integrated system tested. • Second revision with fixes and improvements sent out.
January, 2009	• Second revision of the recording system tested. • We should be able to demonstrate a system that can work on the lab bench. • End of Phase I.
February, 2009	• Begin work on developing an implantable Retinal Recording System.

Table 1: Timeline for the Development of the Retinal Recording System.

Publications

Talks and Posters Presented

J.F. Rizzo, J.L. Wyatt. “Successful Completion of the Boston Retinal Implant Prototype.” talk at the Eye and the Chip World Congress on Artificial Vision, Detroit, MI, June 2008.

D.B. Shire, S.K. Kelly. "Chronic Implantation of a Wireless Subretinal Neurostimulator in Yucatan Minipigs." Poster at the Eye and the Chip World Congress on Artificial Vision, Detroit, MI, June 2008.

G. Swider, W. Drohan, S.J. Kim, J.F. Rizzo, S.K. Kelly, J.L. Wyatt. "Development of a Wireless Neural Recording System." Poster 1772 at The Association for Research in Vision and Ophthalmology (ARVO), April 2008.

J.F. Rizzo, J. Chen, D.B. Shire, S.K. Kelly, M.D. Gingerich, G. Swider, W. Drohan, J.L. Wyatt. "Implantation of a Wirelessly Powered Subretinal Prosthesis Using an *ab externo* Surgical Technique." Poster 3027 at ARVO, April 2008.

D.B. Shire, S.K. Kelly, M.D. Gingerich, O. Mendoza, G. Swider, W. Drohan, J. Chen, J.F. Rizzo, J.L. Wyatt. "Operation of a Wirelessly Powered Subretinal Neurostimulator." Poster 3031 at ARVO, April 2008.

W.A. Drohan, S.K. Kelly, J.F. Rizzo, J.L. Wyatt. "External Field Firing Thresholds for Neurons." Poster 3032 at ARVO, April 2008.

M.D. Gingerich, R. Akhechet, D.B. Shire, J.L. Wyatt, J.F. Rizzo. “Development of a Flexible High-Density Multi-Layered Metallization Interconnect Technology for a Subretinal Prosthesis.” Poster 3035 at ARVO, April 2008.

J.L. Wyatt, Jr., S. Valavanis, Y.-C. Wu, S. Nemati, A. Eisenman, S. Fried, S. Stasheff, J.F. Rizzo. “A Likelihood Method for Estimating Visual Motion Parameters from Retinal Ganglion Cell Responses.” Poster 3043 at ARVO, April 2008.

Theses

S. Valavanis. “Algorithms for Estimating Visual Motion Parameters from Ganglion Cell Responses.” M.S. Thesis, Dept. of EECS, MIT, Jan 2008.