

## **The Retinal Implant Project**

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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, and the VA Boston Healthcare System, as well as 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.

For many years our group acted as a small research center for the interesting problems facing retinal prostheses, content to allow companies, when the appropriate time came, to handle prototype development of FDA-approved experimental implants. In December of 2002, we changed our direction, expanded our group, and are now working to develop our own prototype for chronic implantation. This is a substantial effort, involving fabrication of flexible substrates and electrode arrays, circuit design, biocompatible and hermetic coatings, development of surgical procedures, and vendor development of RF coils and assembly processes. Our hope is to have a prototype chronically implanted in an experimental animal by Fall of 2004.

## 1. Prototype Retinal Implant Development

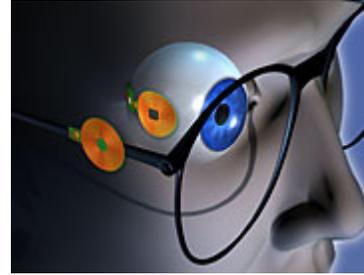
### Sponsors

National Science Foundation Contract BES-020-1681  
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MOSIS provided IC fabrication

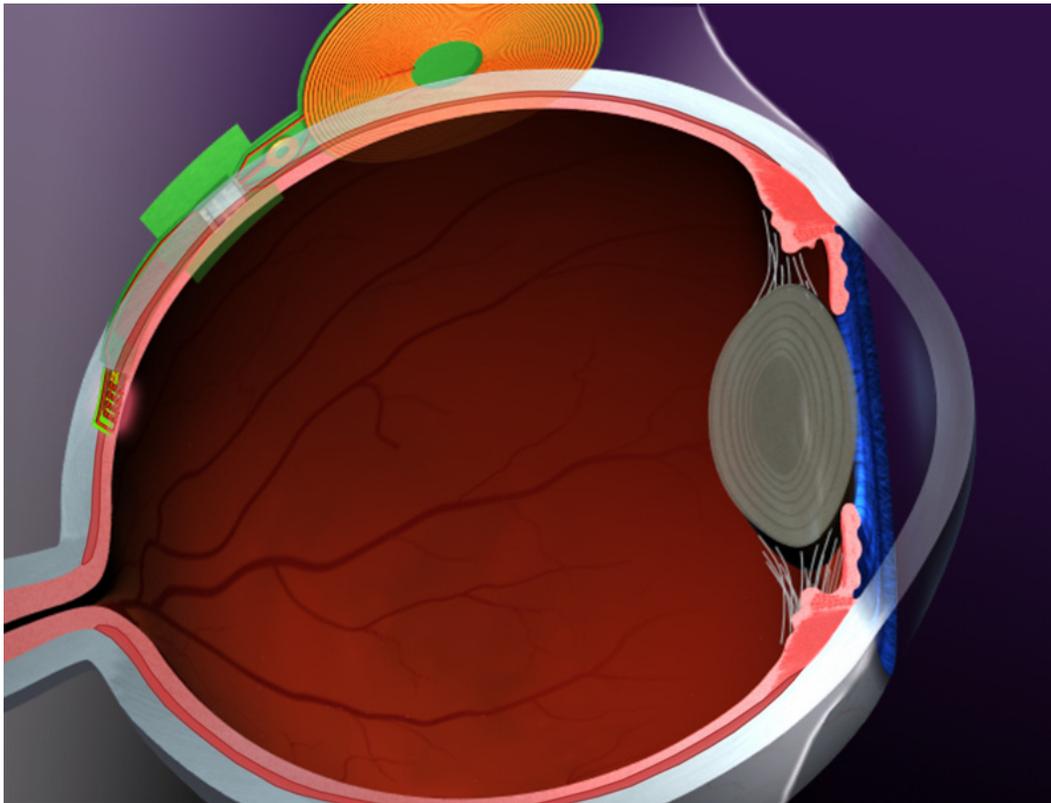
### Project Staff

Luke Theogarajan, Mariana Markova, Milan Raj, Dr. Ofer Ziv, Dr. Shawn Kelly, Dr. Douglas Shire, Dr. Marcus Gingerich, Dr. Carmen Scholz, Dr. Stuart Cogan, Professor John Wyatt

A prototype retinal prosthesis is being developed which will be suitable for chronic animal implantation. This device will attach outside the eye to the sclera, the tough, fibrous wall of the eye (Figure 1). An electrode array will extend through a scleral flap into the subretinal space near the back of the eye to stimulate the retina from beneath (Figure 2). The foundation of the prosthesis will be a flexible parylene substrate with metal traces, serving as a circuit board. Attached to that will be an analog and digital VLSI chip handling communication, control, and stimulation, the necessary discrete electrical components, RF data and power secondary coils, and a flexible parylene electrode array (Figure 3).

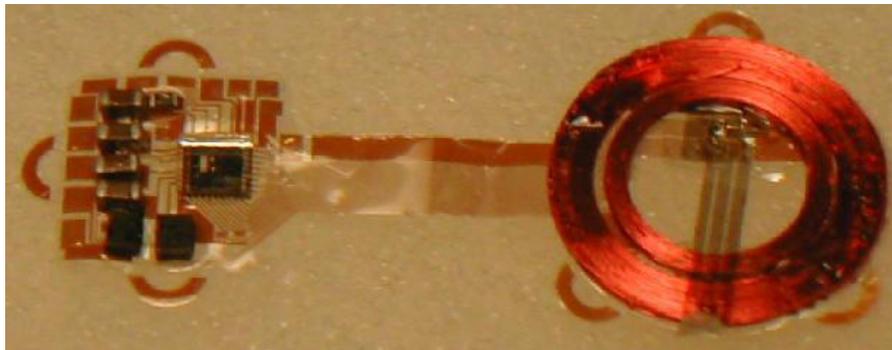
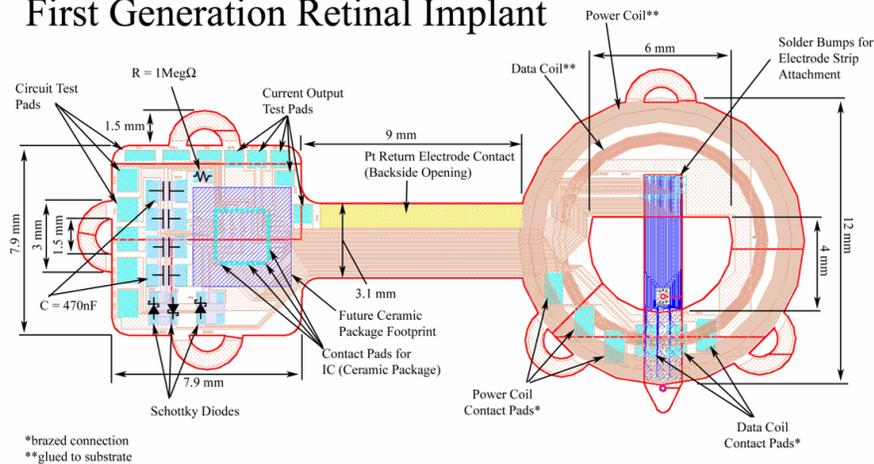


**Figure 1:** Retinal Implant Concept and Placement



**Figure 2:** Subretinal Insertion Via a Scleral Flap

## First Generation Retinal Implant

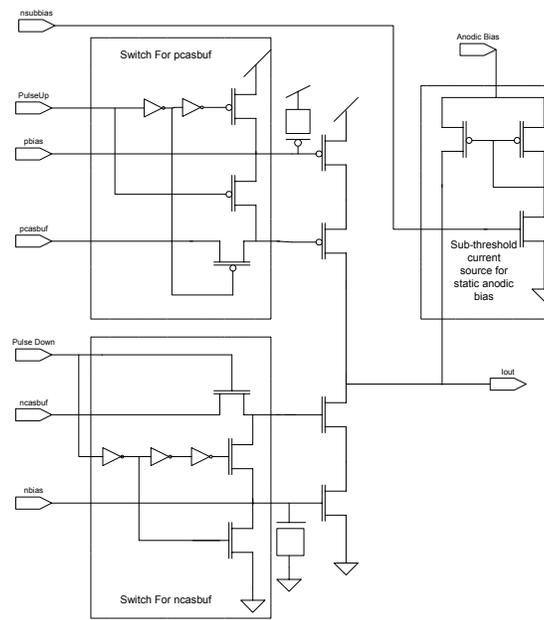


**Figure 3:** First Generation Retinal Implant Design and Implementation

**Flex Circuit Design** – The substrate shown in Figure 3 was designed and fabricated by Doug Shire and Marcus Gingerich at Cornell University. It is made of parylene, with gold wire traces, and is between 10 and 25  $\mu\text{m}$  thick. The electrode array consists of 15 electrodes, each 400  $\mu\text{m}$  in diameter and made of iridium oxide, known for its ability to safely deliver large charge densities to tissue. Similar electrodes were used in our group's acute human surgical trials between 1998 and 2000. First generation flex circuits and arrays have been fabricated and tested, and a second generation is being fabricated which will address some surgical concerns and facilitate testing. A third generation is being designed which combines the flex circuit and array in one piece, eliminating the ball-bump connection between the flex circuits and arrays in the first and second generation designs.

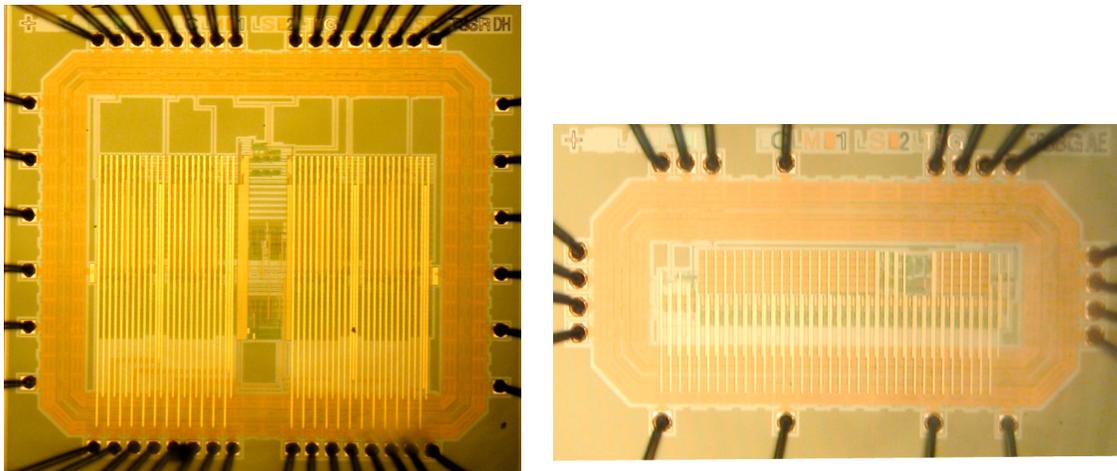
**Chip Design** - The first-generation stimulator chip, designed by Luke Theogarajan, is nearly complete. The chip receives power and stimulation data from outside circuitry, and can drive current through 15 independent electrodes. Power and data are transmitted as radio signals with very different frequencies in order to reduce interference. The data is first filtered to try to remove as much of the power signal interference as possible. It is then interpreted via a delay locked loop (DLL), which locks to the frequency of the incoming data, and uses the pulse duty cycle to distinguish ones and zeros. This method of amplitude shift keying (ASK) is sensitive to interference from the power signal, so frequency shift keying (FSK) and other communication methods are being explored as well. The ASK communication link is capable of transmitting 500 Kb/s on a 13.56 MHz carrier.

Fifteen independent current sources provide the drive for the electrodes. Each has 5-bit programmability, and 2 different operating ranges. The low range spans from 6.25  $\mu\text{A}$  to 200  $\mu\text{A}$ , while the high range spans from 50  $\mu\text{A}$  to 1.6 mA. The schematic in Figure 4 shows one branch of



**Figure 4:** Current driver schematic

a current source circuit. The anodic bias circuit uses a low current, high impedance source to draw the electrode resting potential up to a positive bias with respect to the surrounding tissue, thereby allowing the electrodes to safely deliver more stimulus charge. Micrographs of test chips with the current driver (left) and delay locked loop (right) are shown in Figure 5.



**Figure 5:** Chip micrographs of current driver (left) and delay locked loop (right)

The architecture of the entire chip is shown in Figure 6. The analog front end receives, filters, and demodulates the incoming data, which is then sent through the clock and data recovery unit. The control logic includes a state machine to interpret incoming instructions, which set the amplitudes for the current sources and the timing controls for stimulation. This design gives substantial flexibility in all stimulus parameters: stimulus pulse duration, current amplitude, adjustable anodic electrode bias, and choice of whether the cathodic or anodic pulse comes first.

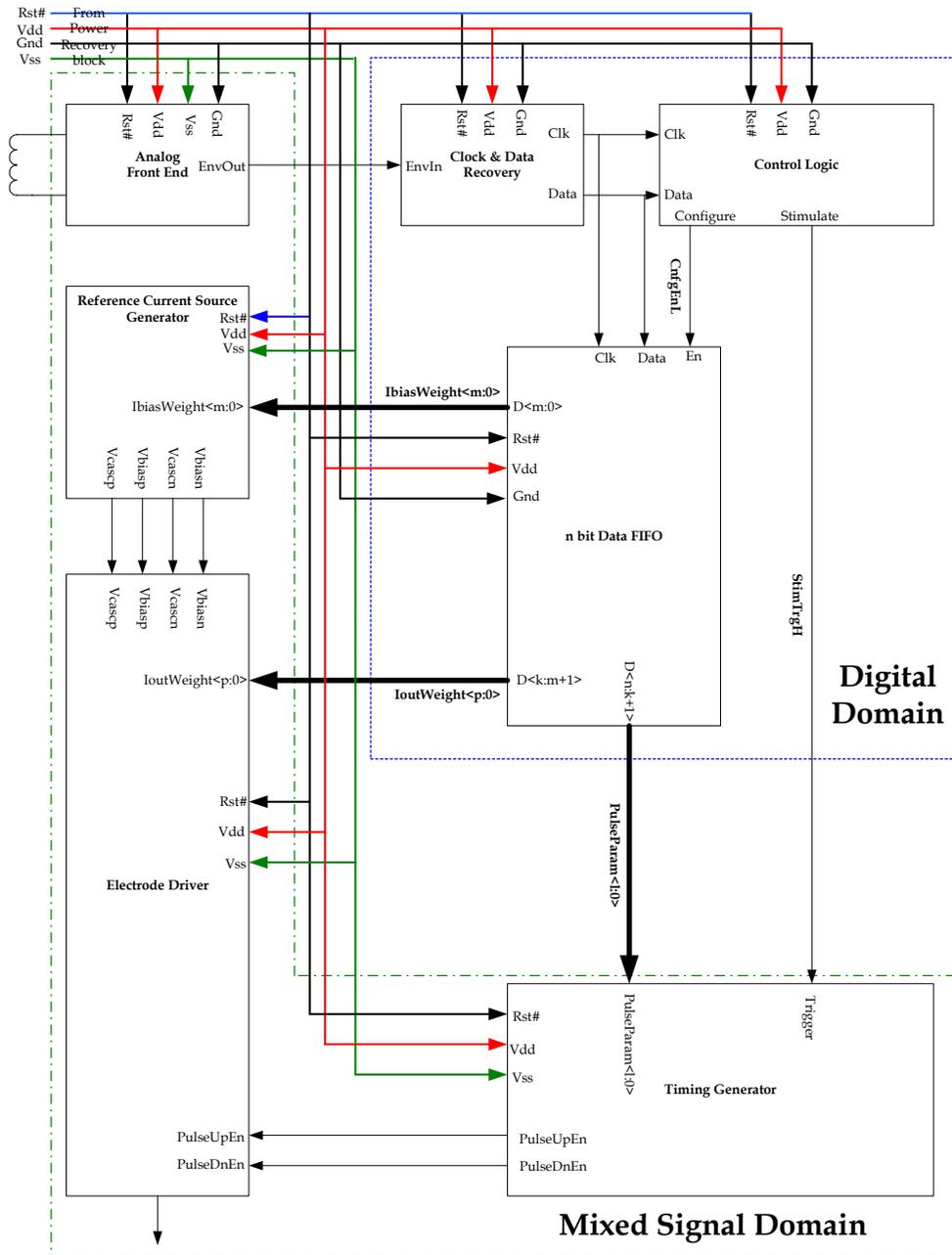


Figure 6: Overall chip architecture

**RF Transmitters** - In addition to the chip, the power and data transmitters have been designed and built by Mariana Markova. The power transmitter uses a very efficient class E circuit to drive the power primary coil, while the data transmitter uses a linear class A circuit. In the initial version of the implant using artificially generated images, data are fed to the transmitter circuit by a computer-controlled modulation system designed by Milan Raj.

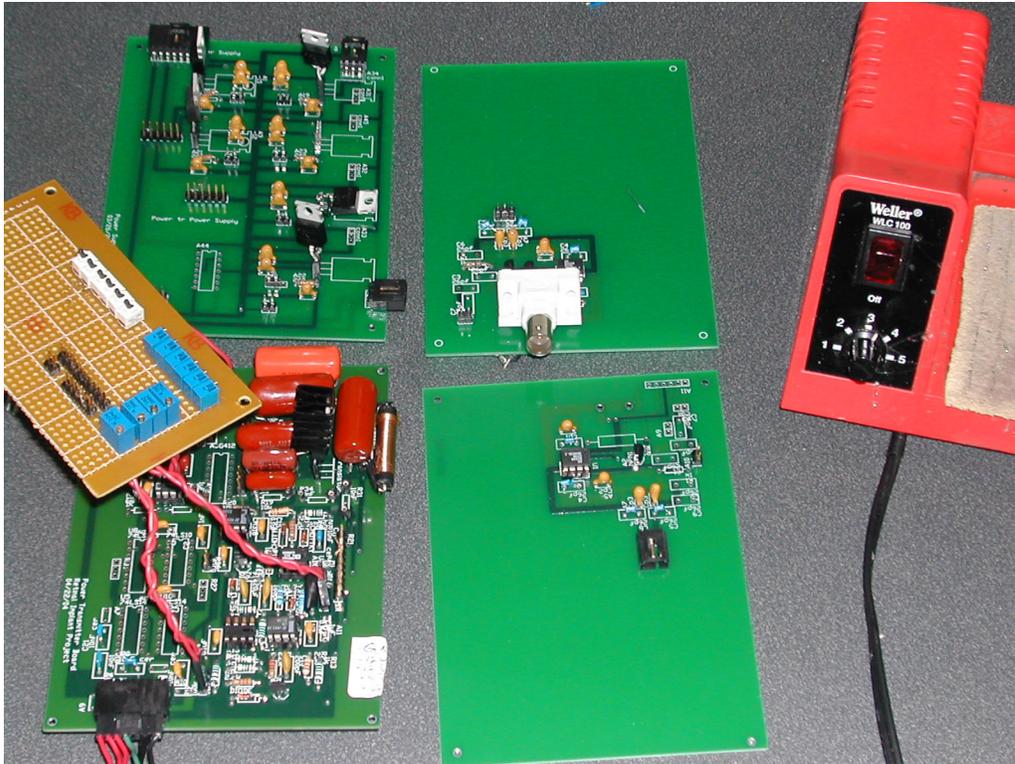


Figure 7: RF Transmitter Boards Being Assembled

**Testing** - Testing protocols have been developed for the chips, as well as for the flex substrates and electrodes. These tests, done with probe stations, single probes, and test jigs in our lab, verify the function of the implant components.

The chips are tested by Milan Raj in a probe station, as shown in the two photos in Figure 8. Probes contact each pad of the chip, and signals can be sent to the chip or measured from the chip. Several test chips have been designed so far. One type of test chip has metal or polysilicon resistive connections to a central metal node. This allows testing for open-circuit connections in the assembly, often due to a bonding problem between the chip and the flex substrate. Another type of test chip includes several transistors, and the threshold voltage ( $V_t$ ) of the transistors is measured. A transistor's  $V_t$  is expected to be very sensitive to any sodium

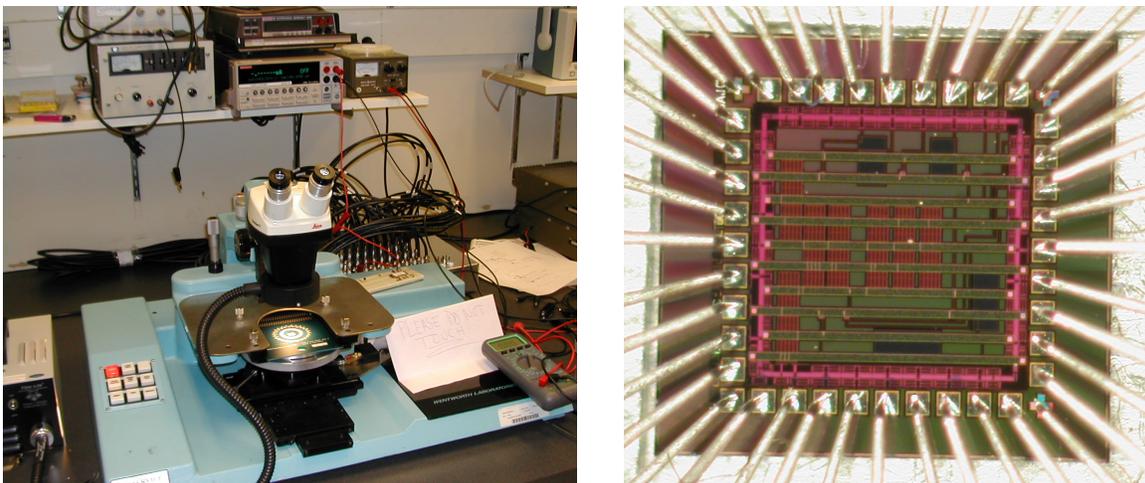


Figure 8: Probe station (left) and chip under test (right)

incursion, so such a chip will be useful in soak testing the implant. Flex substrates, electrode arrays, and assembled implants are tested manually with single probes, as shown in the photo in Figure 9.

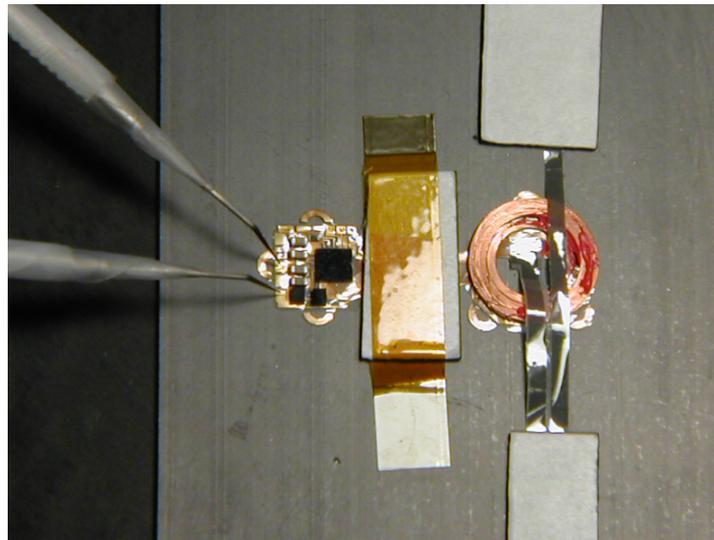


Figure 9: Assembled implant under test

## 2. Low-Power Electrical Neural Stimulation

### Sponsors

Catalyst Foundation Fellowship  
National Foundation Contract BES-020-1681

### Project Staff

Dr. Shawn Kelly, Professor John Wyatt

Traditional current sources for neural stimulation waste substantial energy in supplying electrode current. We have designed a stimulation system with a novel architecture to drive the electrodes

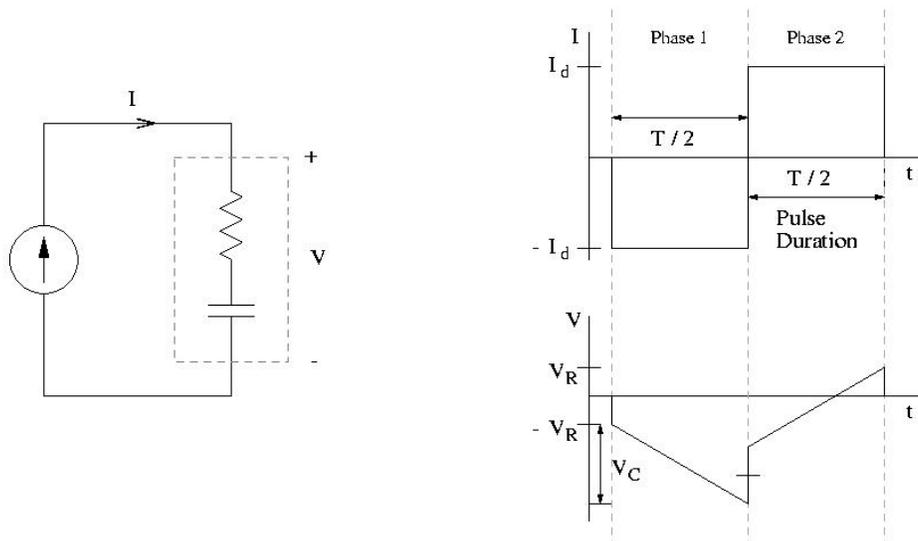


Figure 10: Electrode Drive Current and Voltage Waveforms

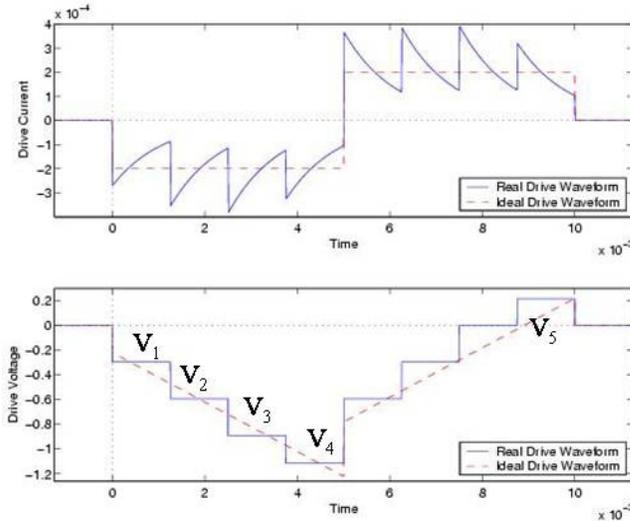


Figure 11: Waveforms for low-power current driver

using a sequence of voltage steps, charging the electrode capacitance with the same total stimulus charge used in traditional current sources, but with much lower energy. The fundamental idea is to charge the intrinsic capacitance of the electrodes without producing large voltage drops across resistances in series with the electrodes. During the discharge phase, the system recovers some of the energy stored in the electrode capacitance. The resulting average stimulation power is about 1/3 the power used by the most efficient stimulators in use today, and less than 1/2 the power of a stimulator using the same voltage sources (which would represent a very aggressive current source design). Figure 10 shows a representative current source driving a series resistor and capacitor, a reasonable model for our iridium oxide

electrodes. The biphasic square pulse current waveform is shown at right, and below that, the resulting voltage waveform. A traditional current source would use transistors in series with the electrode to limit the current. These transistors would carry the entire stimulation current, and would support the sometimes large voltage drop from the supply to the electrodes, resulting in wasted power. The theoretically optimal way to drive the electrodes would be with a voltage source which varies in the step-ramp pattern of the voltage in Figure 10, or at least approximates that voltage. This can be accomplished with a series of voltage steps, as shown in Figure 11.

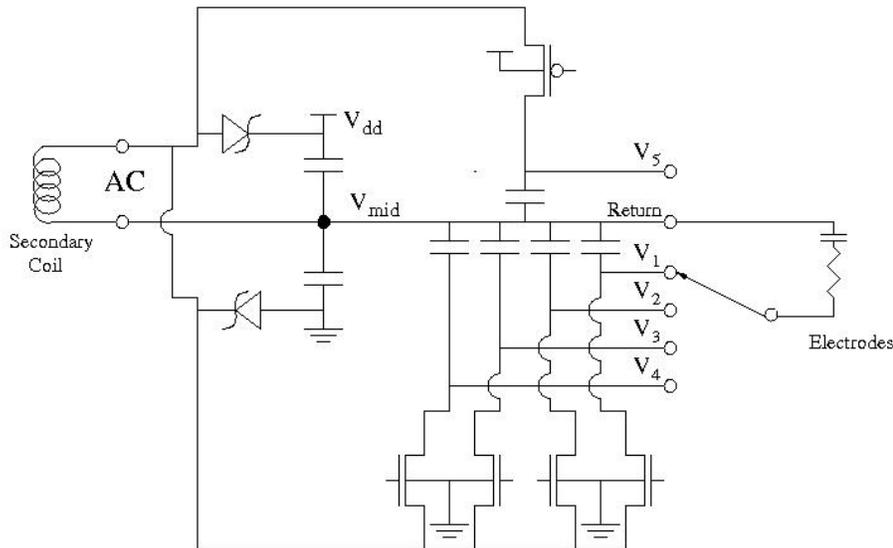
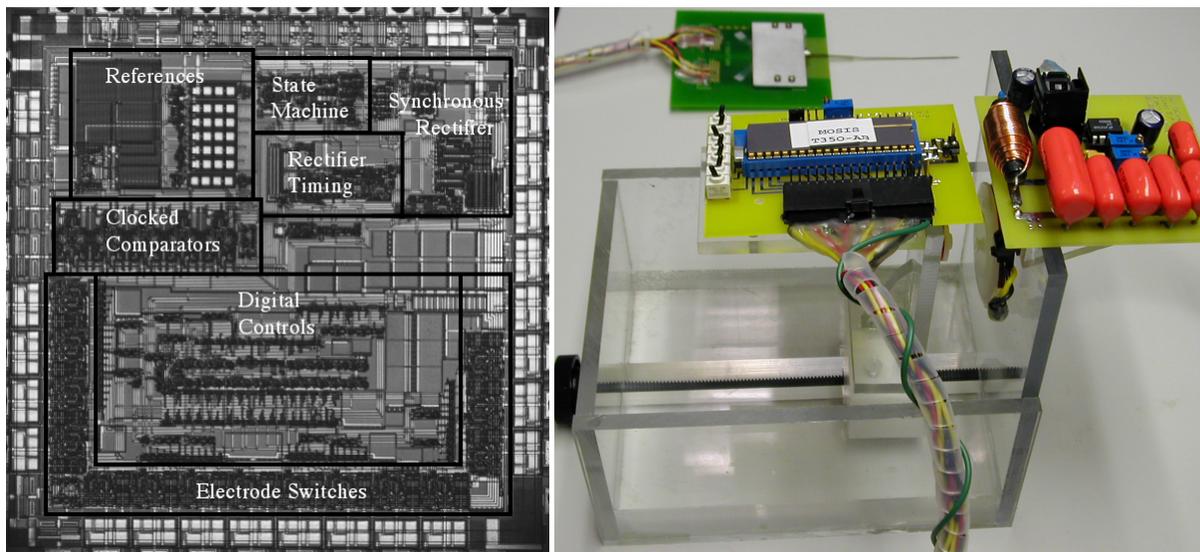


Figure 12: Low-power stimulator circuit

Figure 12 shows a circuit which implements this waveform. A set of capacitors serves as the sequence of voltage steps, and is efficiently generated from the AC power voltage by a carefully controlled synchronous rectifier. This rectifier consists of the five transistors in the figure and substantial control circuitry (not shown), and charges the intermediate voltage capacitors from the power secondary coil at left only when its AC voltage is slightly larger than the voltage of the target capacitor.  $V_{dd}$  and Gnd are generated with respect to the  $V_{mid}$  using standard Schottky diode rectifiers, as shown. The electrodes are switched up and back down the capacitors, delivering the spiking currents shown in Figure 11. This spiking current may be reduced or eliminated by drawing charge from the intermediate voltages not through switches, but through linear-mode transistors acting as current sources, at very small power cost. In other words, the electrodes are being driven by current sources, as in the existing circuit, but the current sources derive their power from low-voltage intermediate sources, saving substantial power. This circuit has been built as a part of Shawn Kelly's PhD thesis, and the system is shown in Figure 13.



**Figure 13:** Stimulator chip and system photographs

### 3. Potassium-Based Neural Stimulation

#### Sponsors

Catalyst Foundation Fellowship

#### Project Staff

Luke Theogarajan, Dr. Ralph Jensen, Professor John Wyatt

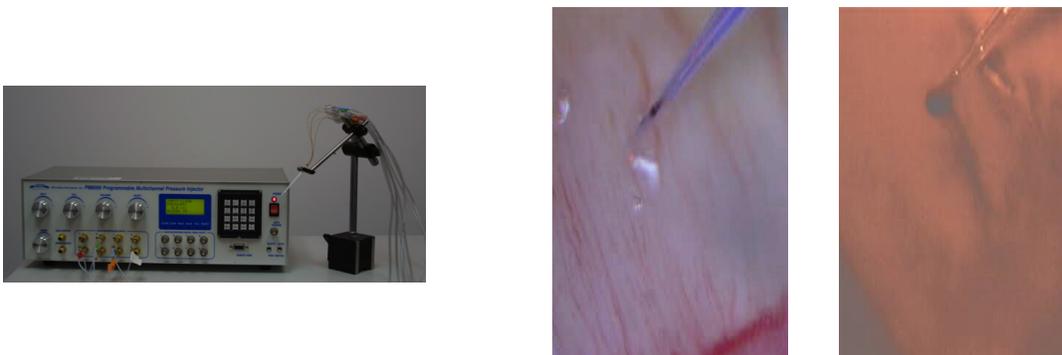
Current neural prosthetic devices use electrical stimulation to excite the neural tissue of interest. Electrical stimulation, though easy to implement, is not the most effective method of neural stimulation. Common problems with electrical stimulation include complex circuitry, lack of focal stimulation, bio-toxicity and high power requirements.

The most natural method to elicit neuronal response is to use chemicals, mainly neurotransmitters. Most neurons generate an action potential when the membrane potential falls below a threshold value. In normal operation this is effected by the binding of the appropriate neurotransmitters at the post-synaptic junction of a target neuron. Though appealing in many

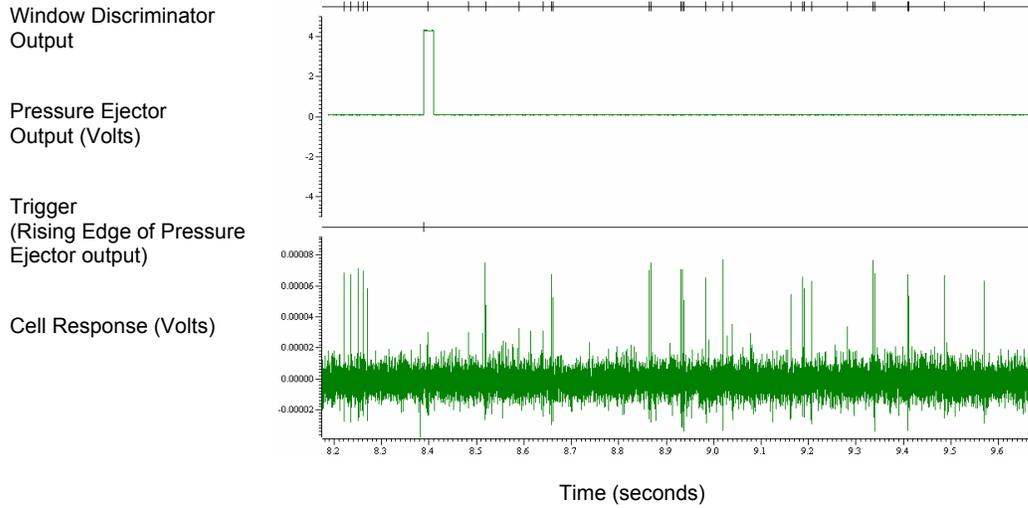
ways, the use of neurotransmitters for stimulating tissue in neural prosthetic devices poses the following problem. The prosthetic device must have an internal mechanism that can generate the neurotransmitter or it must have an internal reserve that will last for the lifetime of the device. Currently many researchers around the world are pursuing the use of neurotransmitter based devices with the idea of using an internal reserve. This poses a major risk since excess neurotransmitter is highly neurotoxic, which may make this method infeasible in practice.

Neurotransmitter, though the most natural chemical method, is not the only way to elicit a chemically mediated neuronal response. We can also evoke a response by changing the membrane potential by modulating the ionic gradients. The membrane potential at rest is determined primarily by the concentrations of potassium ( $K^+$ ) ions, sodium ( $Na^+$ ) ions, and chloride ( $Cl^-$ ) ions in the intracellular and extracellular fluids. At rest, the cell is more permeable to  $K^+$  than it is to  $Na^+$ . By raising the potassium concentration locally around a cell it is possible to depolarize a cell. Ralph Jensen has previously shown that rabbit retinal tissue can be excited by focal application of potassium. We have recently performed experiments to determine the concentration of potassium that would be needed to excite the rabbit retina. These experiments show that a very modest increase in background concentration ( $\sim 10mM$ ) is sufficient to excite the retina.

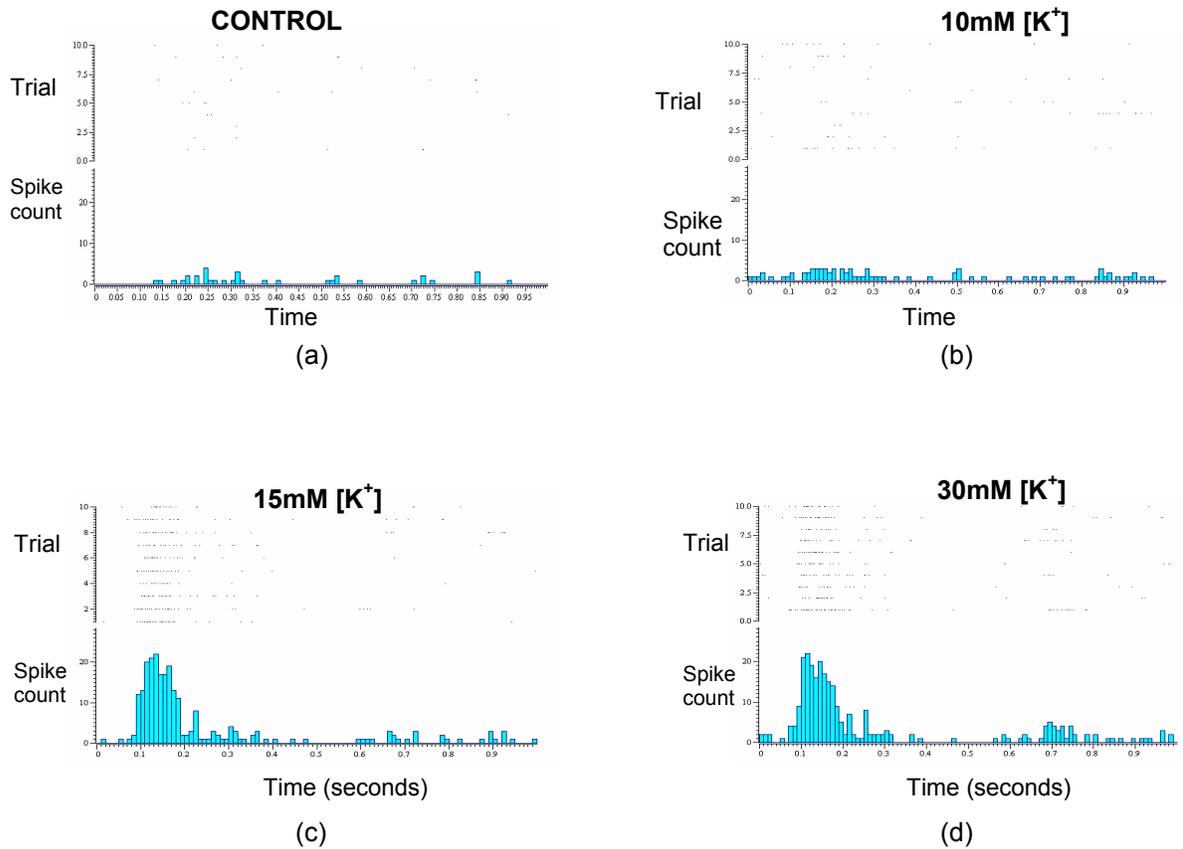
Single-cell recordings were made by Ralph Jensen and Luke Theogarajan from the axons of ganglion cells in an in-vitro rabbit retinal preparation. The ganglion cells were stimulated over the optical receptive field with a multibarrel micropipette containing various concentrations of KCl (0-40mM) in an osmotically balanced NaCl solution ( $\sim 300$  mOsm). All solutions contained Azure B (.5mg/ml) to enable visualization of the solution being ejected as can be seen in figure 14c. Pulse durations of 20-100msecs were used. The control solution (0mM KCl and 150mM NaCl) produced no response, while solutions that contained 10-40mM produced appreciable responses, with response strength increasing with  $K^+$  concentration. Typical response latencies were 30-60msecs after application of  $K^+$ . The recording in Fig. 15 is shown for a 20msec pulse with a potassium chloride concentration of 10mmol. More informative are the peristimulus histograms (PSTH) shown in figure 16. The PSTH is the sum of the individual responses (shown in dark above each plot) that occur within a given time window. For the PSTH's shown, the bin width is 10msecs. Figure 16 a) shows the response due to the control solution, which can be compared to the response due to 10, 15 and 30mM shown in figure 16 b,c and d. The response shows a saturating behavior that is more clearly seen in the graph shown in figure 17. This behavior may be caused by overstimulation of the retina at higher concentrations that causes a refractory behavior. The results indicate that the useful concentration range is between 10-20mM and that potassium is a viable alternative to electrical stimulation for the development of a retinal prosthesis.



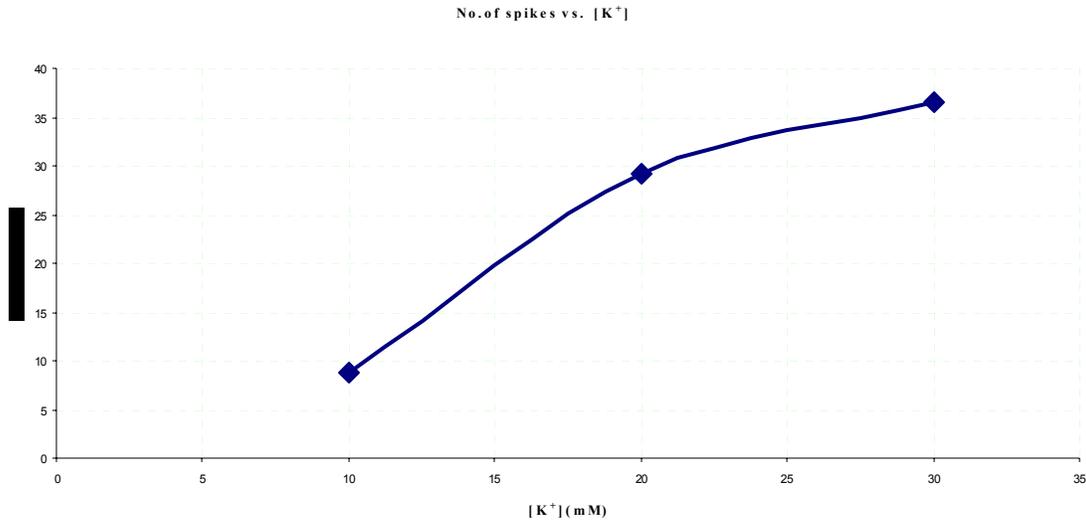
**Figure 14:** Experimental setup a) The multichannel pressure ejector is connected to a 7 barrel micropipette using a luer lock connection b) The multibarrel micropipette over the retina with no ejection of solution under normal lighting conditions c) The pipette ejecting solution under dim red light provided by a LED. The staining of the retina by the dye (AzureB) shows the flow of solution.



**Figure 15:** Typical record from a single cell. Response shown is for a cell stimulated with a 20msec pulse of 10mM  $[K^+]$ , pressure of 40 p.s.i. and a volume of approximately 100pL.



**Fig. 16.** Peri-stimulus histograms(PSTH) for a representative cell stimulated by increasing  $[K^+]$  concentrations. Potassium release begins at  $t = 0$ . A modest increase (10mM) in  $[K^+]$  concentration increases the spike count from 35 to 80 spikes. Further increases in concentration to 15mM and 30 mM increase the spike rate to 240 and 272 spikes, respectively. The histograms are summed responses from 10 trials as indicated by the raster plots in upper part of each figure.



**Fig. 17.** Dose-response curves for various concentrations. Data were collected from 5 cells and the total spike count was obtained from the PSTH. The spontaneous activity (control record) was subtracted, the difference divided by the number of repetitions, and the median is plotted.

## Publications

### Journal Articles, Published

R. Jensen, J.F. Rizzo, O.R. Ziv, A. Grumet, J. Wyatt, "Thresholds for Activation of Rabbit Retinal Ganglion Cells with an Ultra-fine, Extracellular Microelectrode," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 8, pp. 3533-3543, August 2003.

J.F. Rizzo, J. Wyatt, J. Loewenstein, S. Kelly, and D. Shire, "Perceptual Efficacy of Electrical Stimulation of Human Retina with a Microelectrode Array During Short-Term Surgical Trials," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 12, pp. 5362-5369, December 2003.

J.F. Rizzo, J. Wyatt, J. Loewenstein, S. Kelly, and D. Shire, "Methods and Perceptual Thresholds for Short-Term Electrical Stimulation of Human Retina with Microelectrode Arrays," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 12, pp. 5355-5361, December 2003.

### Journal Articles, Accepted for Publication

J.F. Rizzo, S. Goldbaum, M. Shahin, T.J. Denison, J. Wyatt, "In Vivo Electrical Stimulation of Rabbit Retina with a Microfabricated Array: Strategies to Maximize Responses for Prospective Assessment of Stimulus Efficacy and Biocompatibility," *Restorative Neurology and Neuroscience*, forthcoming.

### Meeting Papers, Presented and Published

J.F. Rizzo, R.J. Jensen, J. Loewenstein, J. Wyatt, "Unexpectedly Small Percepts Evoked by Epi-Retinal Electrical Stimulation in Blind Humans," *ARVO Lecture Abstract, Investigative Ophthalmology and Visual Science*, Ft. Lauderdale, FL, May 4-8, 2003, vol.44, abstract 4207.

S.K. Kelly, J.L. Wyatt, "A Power-Efficient, Voltage-Based Neural Tissue Stimulator with Energy Recovery," paper at the International Solid-State Circuits Conference (ISSCC), San Francisco, CA, Feb. 15-19, 2004.

J.F. Rizzo, J.L. Wyatt, J. Loewenstein, S. Montezuma, D.B. Shire, L. Theogarajan, S.K. Kelly, "Development of a Wireless, Ab Externo Retinal Prosthesis," ARVO Lecture Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 3399.

### **Meeting Posters, Published**

S.K. Kelly, J.L. Wyatt, "Low-Power Techniques for a Retinal Prosthesis," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, May 4-8, 2003, vol.44, abstract 5064.

D.B. Shire, M. Gingerich, L. Theogarajan, J. Wyatt, J. Loewenstein, S. Montezuma, J. Rizzo, "Packaging Development for Retinal Prostheses," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, May 4-8, 2003, vol.44, abstract 5084.

S.K. Kelly, J.L. Wyatt, "Low Power Neural Stimulator for a Retinal Prosthesis," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4174.

D.B. Shire, M. Gingerich, S. Retterer, L. Theogarajan, S. Kelly, M. Markova, M. Raj, S. Cogan, J. Wyatt, J.F. Rizzo, "Design and Fabrication of an Ab-Externo Retinal Prosthesis," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4177.

K.J. Karcich, A. Buck, J. Wyatt, D. Shire, M.D. Gingerich, C. Scholz, J. Rizzo, "A System for Leakage Testing of Flexible Electronic Components," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4183.

L.S. Theogarajan, R.J. Jensen, J.F. Rizzo, "Stimulation of Rabbit Retinal Ganglion Cells by Altering K<sup>+</sup> Ion Gradients: Dose-Response Curve," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4215.

M.D. Gingerich, D.B. Shire, K. Karcich, C. Scholz, J. Wyatt, J.F. Rizzo, "Assembly and Packaging Developments for an Ab-Externo Retinal Prosthesis," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4217.

S.F. Cogan, T.D. Plante, J. Ehrlich, D.B. Shire, K. Roach, J.L. Wyatt, J.F. Rizzo, "Charge-Injection Coatings for Flexible Electrode Arrays used in Retinal Prostheses," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, April 25-29, 2004, abstract 4227.

### **Theses**

K. Roach, *Electrochemical Models for Electrode Behavior in Retinal Prosthesis*, M.Eng. thesis, Department of Electrical Engineering and Computer Science, MIT, June 2003.

S.K. Kelly, *A System for Efficient Neural Stimulation with Energy Recovery*, PhD diss., Department of Electrical Engineering and Computer Science, MIT, October 2003.