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, 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. 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, biocompatible and hermetic coatings, development of surgical procedures, and vendor development of RF coils and assembly processes. We plan to have a wireless prototype chronically implanted in an experimental animal in 2007. Our web site, www.BostonRetinalImplant.org gives more information about the project and team.

Development of a First Generation Wireless Implantable Retinal Implant

Sponsors
NIH contract 1-RO1-EY016674-02
VA Center for Innovative Visual Rehabilitation
MOSIS provided IC fabrication

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Over the past several years, we have developed a wireless retinal prosthesis prototype as the first step toward a human subretinal prosthesis. Figure 1 shows an artistic conception of the prosthesis. Power and data are transferred wirelessly to the implant via radiofrequency (RF) fields from the primary transmitter coils to the secondary receiver coils. This approach avoids a
cable connection between the eye and external hardware. Only the electrode array is placed in the subretinal space beneath the retina. A model of the prototype is shown in Figure 2.

**Figure 1.** a) Artist’s conception of the subretinal implant system. The image obtained by an external camera is translated into an electromagnetic signal wire transmitted wirelessly from the external primary data coil to the implanted secondary data coil attached to the outside wall (sclera) of the eye. Power is transmitted similarly. Essentially the entire volume of the implant lies outside the eye, with only the electrode array penetrating the sclera. b) The electrode array is placed beneath the retina through a scleral flap in the sterile region of the eye behind the conjunctiva.

![Figure 1: Artist’s conception of the subretinal implant system.](image1)

**Figure 2.** 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: Detailed mockup of the first-generation implant.](image2)

The core of the retinal prosthesis is the 25,000 transistor stimulator chip, originally designed by Luke Theogarajan, with later revisions by Shawn Kelly, and fabricated at no expense to the project by MOSIS. It was designed for flexibility and can operate at a wide range of externally controlled clock frequencies. The chip produces variable current pulse durations, amplitudes, inter-pulse intervals and selections of the set of electrodes to be stimulated. The first version of the chip worked well enough to be used in the prototype, but over the past year 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 animal work. For the longer term we also need to add a low-bandwidth back-telemetry capability to enable us to monitor electrode voltages and impedances.

The design and some construction and testing steps for other components of the retinal prosthesis have been carried out successfully in-house: these include fabrication of the microelectrode array, fabrication of an initial version of the flexible substrate, an electronic stimulation controller and test system, power and data transmitters, and a very sensitive soak testing system to check for tiny (picoampere) currents due to saline leakage. Other steps were sourced out to vendors: these include coil winding, flip-chip and wire bonding to the substrate, later versions of the polyimide flexible substrate, iridium oxide deposition on the electrodes, prolonged testing of the electrodes under repeated stimulation, and of course fabrication of the stimulator chip.

During the past six years we have radically redesigned the retinal implant. In previous designs the entire implant was intraocular and the electrode array lay on the inner epiretinal side of the retina. We have now adopted a quite different subretinal design, shown in Figures 1 and 2, where almost the entire bulk of the device is attached to the outside wall of the eye. Our surgical experience in animals suggests that this new design has the following advantages: 1) the risks of surgical trauma and infection are minimized since only the stimulating electrode array penetrates the eye, 2) there is no need to attach the electrode array to the retina with glue or tacks since the array is sandwiched between the retina and the pigment epithelium, 3) all electronic hardware is located outside the eye so that the heat-generating electronics is not a threat to retina, 4) the relatively spacious ocular orbit (eye socket) allows us to use thicker standard hermetic encapsulation methods for the external electronics, and 5) threshold currents for stimulation of retinal neurons may be lower since the electrode array is closer to outer retinal neurons. It is noteworthy that with small modifications our subretinal prosthesis can also be converted for epiretinal stimulation, if the need arises.

**Hermetic Package and Feedthroughs**

Our first generation wirelessly driven implant, shown in Figure 3 on the left, was meant to be encapsulated in parylene-C for saline testing and animal implantation. However, soak tests have revealed minor delamination of the parylene coating, as well as corrosion of the exposed metal current return region, as shown in the figure below. This figure clearly shows that this encapsulation method is not suitable for long-term (months or years) animal studies, nor for the clinical studies that will eventually be required.

![After parylene coating](image1.png) ![After 85 days of soaking](image2.png)

*Figure 3. Present implant before saline soak test (left) and section after soak test (right).*
Our preliminary experimental results thus confirmed our proposed justification for the
development of new state-of-the-art hermetic micro-package technology for our retinal prostheses
devices. Our efforts under this proposal have 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 thereby 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. This package is shown in Figure 4,
both in conceptual and prototype form. The hermetic package will allow us to proceed to
longer term animal surgical trials with a 15 electrode implant.

![Figure 4. CAD design of the hermetic feedthrough package (left) and prototype version of the implant before sealing the case (right).](image)

Our overarching objective has been to develop a packaging approach which 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 on the order of 20 feedthroughs
(as our current device does), 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 year, however, is that the pitch between output channels in our current implant (500 microns)
may actually be maintained even if a larger ceramic substrate is used and 100+ pins are placed
through it. In Figure 5, a conceptual sketch of a 104-pin feedthrough in which all the channels are
contained within a ceramic disc 7 mm in diameter is shown.

![Figure 5. 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 Figure 4. The stimulator IC would be located immediately adjacent to
this feedthrough assembly on the inside if the case.](image)
This disc will form part of the lid of a Ti enclosure having a similar form factor to that shown in Figure 4, and 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 the initially-proposed goal of 150 I/O channels may be achievable within a Ti enclosure approximately the same size as that we are currently implanting. Our current plan is continue pursuit of this approach.

**Implant Circuit Testing**

Our first generation implant, shown in Figure 2 above, has been tested on the bench with wireless power and data telemetry while driving electrodes in saline to mimic body tissue. It has also been tested while soaking in saline, with wireless power and data telemetry. Figure 6 shows the implant during this saline test, and the resulting test waveforms.

![Figure 6. First generation implant under test in a bath of saline (left), and telemetry and electrode voltage test waveforms (right).](image)

This first generation implant was coated with a thin silicone layer, which protects it from short duration exposure to saline. However, due to the inability of this coating to survive inside the body for the 10 years required by the FDA, we have pursued a hermetically enclosed version of this implant, dubbed generation 1.5. This implant, shown above in Figure 4, is being tested as pieces are assembled. Figure 7 shows the assembled circuit that will go inside the titanium case, as well as its corresponding bench test waveforms.

![Figure 7. Generation 1.5 implant internal circuit flex (left), and bench test waveforms (right).](image)
Chip Revision

We have also been working to improve the function of our communication and stimulation integrated circuit chip. The chip includes a startup clock circuit which, in the first version, consumed far too much power. The excess power consumption required a substantially stronger magnetic field for power telemetry, which in turn interfered with the magnetic field for data telemetry. Since data reception is necessary to bring the chip out of its reset mode and shut down the startup clock, this was a potentially crippling problem, and impacted the reliability of data transmission.

This problem was solved by replacing the inverter s and NAND gate in the clock’s ring oscillator with current-starved versions, reducing the current draw for this circuit from 20mA to 450μA.

The current source electrode drivers on the chip require an anodic offset voltage of approximately 0.6V to take full advantage of the charge capacity of the iridium oxide electrodes we are using. This offset voltage is loosely coupled to the electrode via a weak current source, which will gently pull the electrode up to the anodic bias point, yet not interfere with the current source driver during a stimulation pulse. The first version of the bias current source was designed with far too little current to be able to pull up the electrode voltage. This current source was revised to be able to deliver approximately 8 times the current available before. We have plans to redesign the bias circuitry to include stronger bias current sources, as well as a feedback controller to better regulate the bias voltage.

Biocompatible Coatings

Our microfabricated electrode arrays will be implanted into the subretinal space, and must be biocompatible. We are working to develop biocompatible coatings to reduce cell growth over the electrode array. These coatings must also adhere to the array and to the interface between the array and the hermetic packaging being developed.

Our preliminary results indicated that poly(ethylene glycol), PEG, showed superior biocompatibility when electrically inactive test strips were implanted in the subretinal space of Yucatan pigs. Thus, we focus on the synthesis of PEG block copolymers, where the PEG moiety provides the biocompatibility, and a second block will be functionalized so it can carry the anchoring groups, that will covalently bind to the hermetic sealant layer.

The PEG is attached to a poly amino acid, such as pLys, pGlu, or pAsp, which is then thiolated to allow for a stable S-Au bond to form between the biocompatible polymer and the gold substrate of the flex circuit.

We have spent considerable effort on the thiolation of our PEG-b-p(aa) copolymers, in order to establish conditions that will allow the coating of the implant surface with these materials. The purification of the synthesis products proved to be quite challenging. However, the deprotection of all PEG-b-pAsp’s and PEG-b-pGlu’s was ultimately performed without polymer degradation as monitored by GPC and 1H-NMR. The process of deprotection was improved by addition of THF to the aqueous 0.2 M NaOH solution, which offered better solubilization to the protected polymer (see Figure 8).
The pure PEG-polypeptides under sodium salt (Figure 8) were then thiolated with cystamine in presence of NHS and EDC as coupling agents (see Figure 9). The amount of cystamine varied between one and two units per 10 carboxylate functions, depending upon the size of the polypeptide block.

A gold surface (simulating an implant) was coated with this polymer by exposing the surface to a 100 μM solution of the thiolated polymer for 10 min, followed by washing the substrate 3 times with pure water, and air-drying. The resulting substrate was imaged by AFM; see Figure 10.
The other achievement in this work is the ring-opening polymerization of N-carboxyanhydride (NCA). This result will improve the gelation of the multi-block copolymers we have synthesized to date.

Forming block copolymers is desirable for our research effort, since amphiphilic block copolypeptides are expected to gel based on intermolecular interactions (see Figure 11). Such ‘living’ polymerizations proceed in general in the following manner. The polymerization of all chains starts at the same time, provided that the rate of initiation >> rate of propagation. The growing chains remain active after the consumption of one monomer, thus allowing for the successive polymerization with additional monomers, and the eventual formation of block copolymers.

![Figure 10. AFM photos. Left: pure gold. Right: polymer-coated (PEG-b-pGlu M/I= 70) gold.](image)

**Figure 11. Principle of NCA polymerization.**

**Surgical Technique Refinement**

Experiments were conducted to refine our technique for ab externo subretinal placement of microelectrode arrays in Yucatan minipigs.

Our past implant configuration was too large to be fully covered by the conjunctiva and Tenon’s capsule. As a result, the entire layout of the implant was modified. We conducted several fittings of plastic mockup designs in porcine eyes. Once a favorable design was developed, we implanted full scale mockups with titanium cases and wound secondary coils. Our initial implants in live pigs developed exposure and partial extrusion. This resulted from conjunctival necrosis.
over the titanium case, and exposure of the anterior coil due to tension on the conjunctival/ Tenon's closure. Covering the titanium case with a thin layer of silicone helped prevent conjunctival necrosis. Moving the case further posterior in the orbit helped with this and with early exposure, but there was still too much tension on conjunctival closure. We then tried creating a large half thickness scleral flap in the quadrant where the titanium case was placed. The flap started about 8 mm posterior to the muscle insertions, and was carried forward to approximately 2 mm posterior to the limbus. The anterior coil and titanium case were placed under the flap. Conjunctiva in this quadrant was sutured to the edges of the flap, so that there was virtually no tension in the closure. We now have 2 pigs with successful implants and no exposure using this technique. One pig has survived 2 months without exposure or extrusion.

Also, in the past year we implanted a 5 mm diameter microfabricated electrode array beneath the retina of three Yucatan mini pig eyes. All pigs were kept alive for three months after surgery with no severe complications. This is the largest implant that has been implanted under the retina. Theoretically this device would allow a patient to see over approximately 23 degrees of visual angle, which is equal to roughly half of the normal amount of nasal visual field.

![Figure 12. Surgical implantation technique.](image)

Deciphering the Retinal Neural Code for Motion

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**Background and Hypotheses**

Our project is to study the neural coding of visual data in retinal ganglion cells. The goal is to provide a rational basis for algorithms for electrical stimulation of the retina in a retinal prosthesis. Our approach has been to expose the retina to a moving visual scene and then attempt to reconstruct the scene from ganglion cell firing data recorded with a multi-electrode array.

Our immediate goal for the past year has been to understand what information is available at the Retinal Ganglion Cell (RGC) level (i.e. before this information is processed by the brain) in response to moving bars. Our approach has been to optically stimulate a rabbit retina with moving bars which vary in speed, angle of movement, and size, and to record the RGC responses with a Multi-Electrode Array (MEA).
Given only the above recordings, we attempted to estimate the speed and angle of the moving bars. The first part of the data analysis was classifying the recorded cells according to their function; in our estimation algorithms, we used three types of cells: ON cells (cells that respond to bright bars), OFF cells (cells that respond to dark bars), and Directionally Selective (DS) cells (cells that respond maximally to bars moving in their preferred direction and respond minimally to bars moving in the opposite of their preferred direction).

We have the following hypotheses about the results of using ON/OFF cells and DS cells in motion estimation algorithms:

1. The accuracy of speed and angle estimates using only the information carried by the ON/OFF cells increases as we increase the number of these cells used in the algorithms.

2. The accuracy of speed and angle estimates by using only the information carried by the ON/OFF cells decreases as the ON/OFF cells used become more clustered (i.e. less spread out).

By combining 1 and 2 from above, we hypothesize that speed and angle estimates would lose accuracy if we confine attention to ON/OFF cells in a small region of the retina, where the cells will be closely clustered and fewer in number. If so, it would follow that ON/OFF cells are adequate for estimating motion parameters of global motion (i.e. for estimating speed and angle of large moving bars) but are inadequate for estimating motion parameters of local motion (i.e. for estimating speed and angle of small moving bars). This leads us to formulate our third hypothesis:

3. ON/OFF cells are not adequate for local motion estimation, and DS cells must also be used to estimate local motion parameters.

Results

We have devised algorithms to estimate the angle and speed of moving bars by using only ON/OFF cells. We have tested the algorithms both on retinal data obtained from multi-electrode array experiments and have also tested them with numerical simulations. The simulation data in Figure 13 shows that the estimates deteriorate as the ON/OFF cell population decreases and as the cells become more clustered. We have verified that these trends are in line with theoretical predictions and have proved that angle and speed estimate errors are proportional to the proximity of the cells and to the number of cells. We have also observed the same phenomenon in tests with multielectrode array data from rabbit retina.
We have also devised an algorithm to estimate the angle of moving bars using only DS cells. Simulation data in Figure 14 shows that the angle estimates deteriorate as the number of DS cells used decreases and as the "noise" in the directional selectivity (some DS cells have a wider range of preferred angles) of a DS cell increases.

**Figure 13.** Results of Estimating Speed of a broad moving bar using ON/OFF cells.
We are currently trying to verify the results of Figure 2 theoretically. We are also currently trying to merge the ON/OFF algorithms with the DS cell algorithm and examine the behavior of the resulting "mixed" algorithms.

**Publications**

**Presented**


**Theses**