

The Retinal Implant Project

RLE Group

Retinal Implant Research Group

Academic and Research Staff

Professor John L. Wyatt, Jr.

Visiting Scientists and Research Affiliates

Joseph Rizzo, M.D., Dr. Shawn Kelly, Dr. Ofer Ziv

Graduate Students

Luke Theogarajan, MS, Mariana Markova, MS, Antonio Molins, Adam Eisenman

Technical and Support Staff

Barry Yomtov, Bill Drohan, Greg Swider

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 2005. 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-EY016674-01

VA Contract V523P-7057, and other VA support

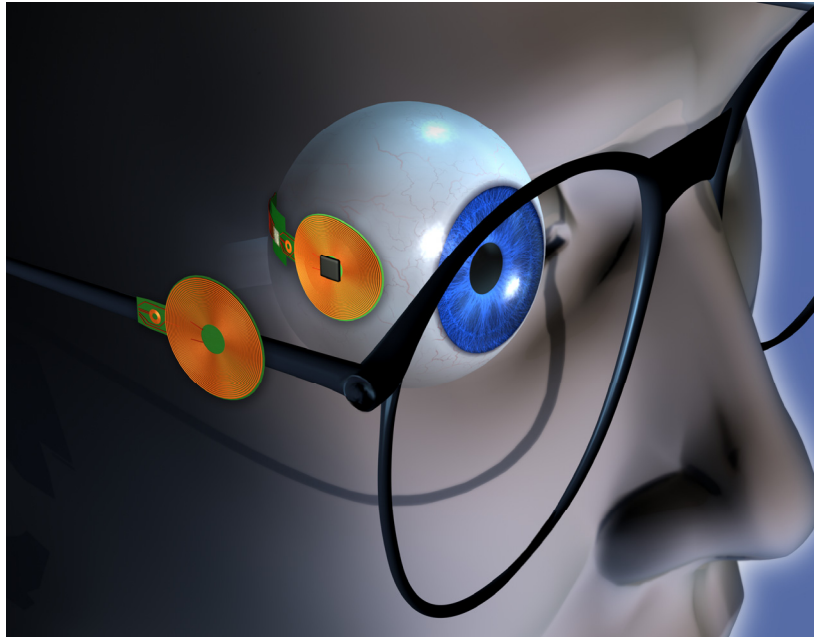
Catalyst Foundation Fellowship

MOSIS provided IC fabrication

Project Staff

Barry Yomtov, Bill Drohan, Greg Swider, Luke Theogarajan, Mariana Markova, 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. 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.



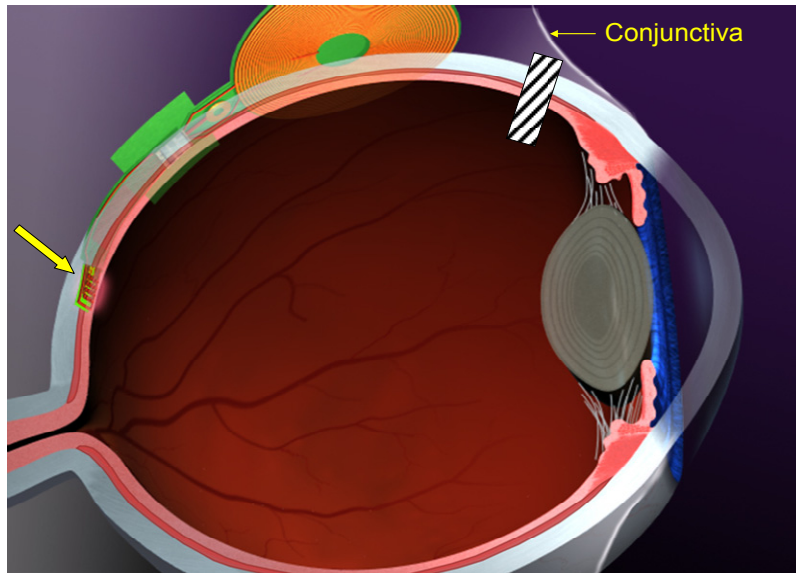


Figure 1. a) Artist's conception of the subretinal implant system. The image obtained by an external camera is translated into an electromagnetic signal wire transmitted wirelessly from the external primary data coil to the implanted secondary data coil attached to the outside wall (sclera) of the eye. 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.

Mockup of First Generation Implant

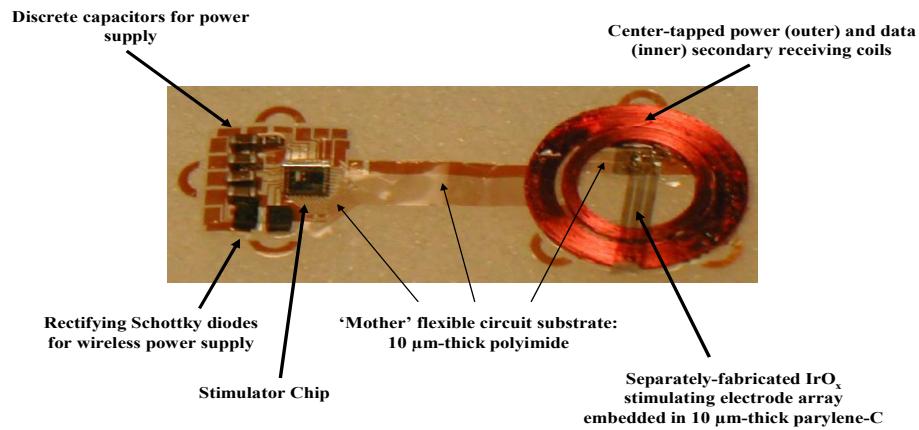


Figure 2. Detailed mockup of the first-generation implant. All parts are mounted on a 10-um thick flexible substrate, which has conducting wires embedded within. The thin neck is placed beneath the superior rectus muscle during implantation. The implant is sutured to the sclera through the six semicircular tie points shown.

The core of the retinal prosthesis is the 25,000 transistor “stimulator chip, designed by Luke Theogarajan 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 five 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.

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 then 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. One scheme for creating the thiolated copolymer is shown below in Figure 3.

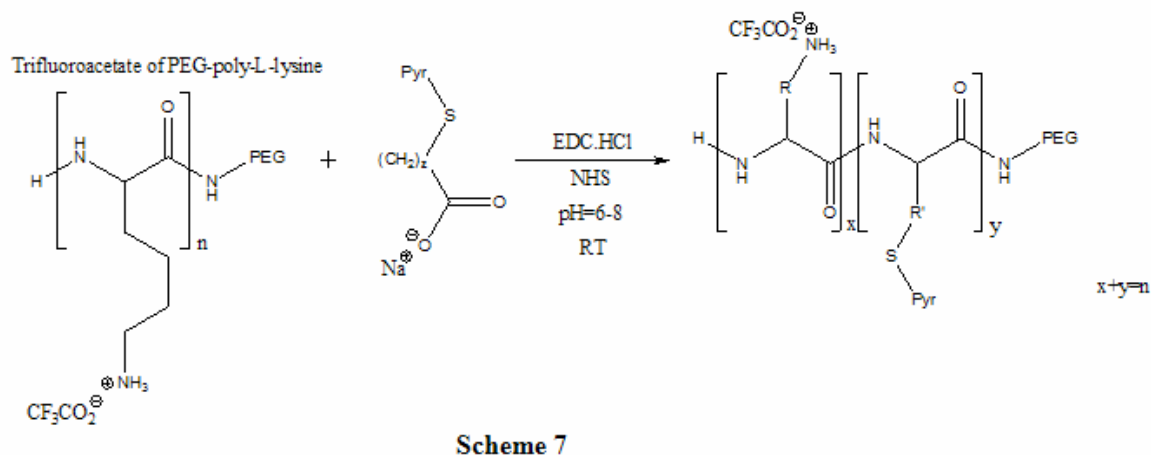


Figure 3. Thiolated copolymer synthesis scheme

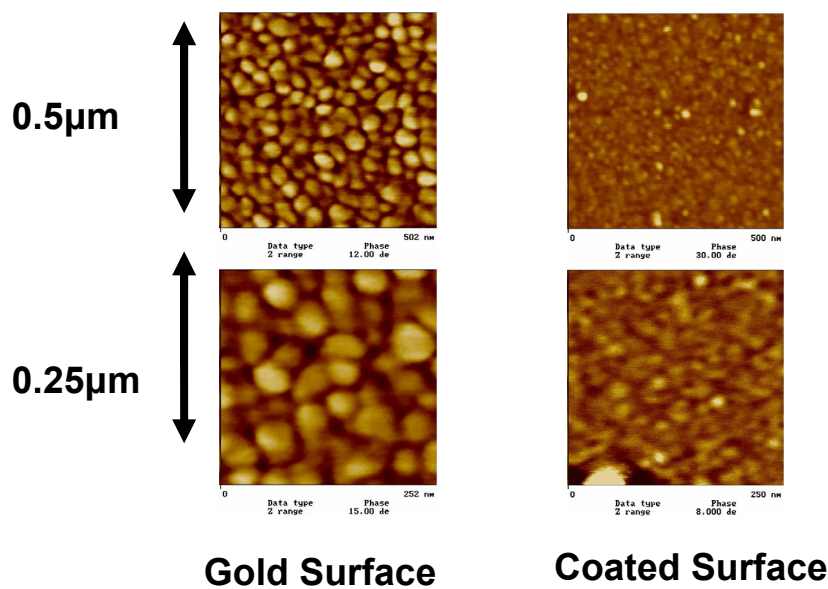
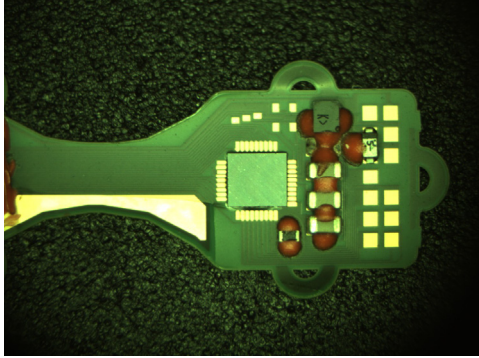


Figure 4. Atomic force microscope photographs of uncoated (left) and coated (right) gold surfaces.

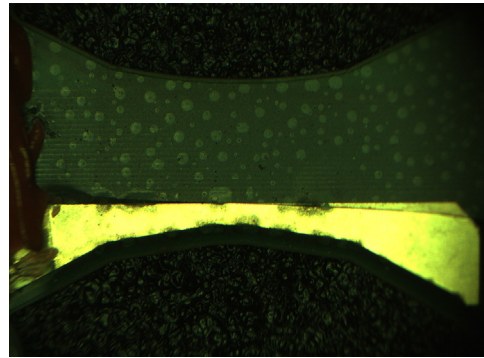
Figure 4 above shows that the thiolated block copolymer covers a gold surface without any defects on a micron scale. The left side shows an AFM phase image of a gold surface, at two different magnifications. The right side shows the gold surface covered by a thiolated block copolymer.

Hermetic Package and Feedthroughs

Our present wirelessly driven implant, shown in Figure 5 on the left, is 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



After 85 days of soaking

Figure 5. Present implant before saline soak test (left) and section after soak test (right).

Our preliminary experimental results thus confirm our proposed justification for the development of new state-of-the-art hermetic micro-package technology for our retinal prostheses devices. To date, our efforts under this proposal have focused primarily on the conceptual and paper design 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 feedthrough, shown in Figure 6, below, and its associated hermetic package, will allow us to proceed to longer term animal surgical trials with a 15 electrode implant. A 100 channel device is being designed for future work and clinical trials.

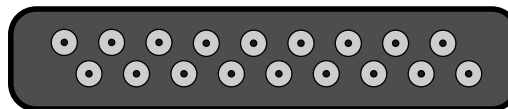


Figure 6. Ceramic hermetic feedthrough

Surgical Technique Refinement

Experiments were conducted to refine our technique for ab externo subretinal placement of microelectrode arrays in Yucatan minipigs. Successful refinements included: a) use of the Elman Surgitron for cautery of the choroid, b) sharp incision of the choroid with more controlled insertion was possible after using the Surgitron, c) use of hypotensive anesthesia reduced choroidal hemorrhage, d) use of a 41 gauge subretinal needle allowed more controlled creation of a local retinal detachment at the insertion site.

An alternative technique for microelectrode insertion in minipigs was developed. This technique was modeled after a technique used for en block excision of choroidal tumors in humans. Hypotension was maintained by IV nitroprusside. A large partial thickness scleral flap was created. To lower intra-ocular pressure, vitrectomy and paracentesis were performed. Scleral fibers were shaved away to expose the choroid; a choroidectomy was made by tenting the choroid with a forceps and removing the tissue with a scissors. Healon was injected in some eyes through a choroidotomy into the sub-retinal space to separate the choroid and retina. An inactive, gold-wired polyimide strip was placed onto the retina and the scleral flap was sutured. In 4 eyes, the surgery failed because of a significant choroidal hemorrhage and retinal tear. In 7 eyes, a large area of retina (> 6 x 3 mm) was exposed and an array was successfully implanted in 5 of these eyes (In the other 2 eyes, an area of retina was exposed but the eye collapsed thereafter because of marked ocular hypotonia). In 3 eyes, the area of exposed retina was not large enough for the 1.5 mm wide electrode array. More work is needed to develop this technique, but this procedure may be a viable alternative method for prosthetic implantation.

We tried a dog model for prosthesis implantation. Other groups have used this model for epiretinal implantation and have reported electrically evoked cortical potentials. In general the eye surgery went as well as in pigs, but adequate VEPs could not consistently be recorded. The anatomy of the dog visual cortex is not well known.

Insertion of Electrode Array

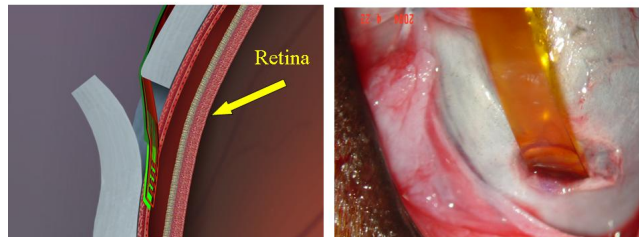


Figure 7 Surgical implantation technique.

Implantable Wireless Neural Recording Device

Sponsors

National Science Foundation
NSF No.: IIS-0515134

Project Staff

Mariana Markova, Luke Theogarajan, Professor John Wyatt

Overall Goal

The overall goal of this project is a neural recording system designed to acquire and process neural spikes from a large number of recording electrodes (256 currently). The system should be able to record the ganglion cell output under both light and electrical stimulation. The close proximity of the stimulating and recording electrodes force the device to work in the presence of large stimulus current pulses which generate signals (stimulus artifacts) at the recording electrodes on the order of 100 times larger than the input signal of interest. The design should be scalable in terms of addition of new input channels so that it can address up to 1000 electrodes with no significant increase in the power budget. The goal of the system is to satisfy the requirements of an implantable device in terms of power, area and number of accessible inputs while capable of transmitting the signal through a wire to a receiver for an in vitro test. Design and optimization of a wireless transmitter are a subsequent goal for the project to make the implantable device complete.

Amplifier Design Challenge

The past year's work has focused on a low-power amplifier to record neural signals in the presence of large stimulus artifacts. The primary concerns are accuracy and the low power consumption required for an eventually implantable device. The spike signals have amplitudes of 50 μ V to 500 μ V while the stimulus artifact (SA) can be as large as 100mV. (Figure 1) Design specifications are given in the table below. It is not possible to remove the stimulus artifact by filtering because the artifact and neural action potentials have components in the same frequency band (Figure 2). Ideally the large input signal should be attenuated while the small superimposed spike preserved. The central issue is that 17 bits of accuracy are necessary to resolve a spike of 50 μ V superimposed on a SA of 100mV. The major design challenge is that the total power budget for an implanted device would not suffice for even a single input channel meeting a 17bit accuracy requirement.

Input Signal:	30 μ V-500 μ V
Range	10Hz-10KHz
BW	256
Number of input signals	
Stimulus Artifact:	1mV-100mV
Range	DC -<10KHz
BW	
Total Power Budget	~4mW

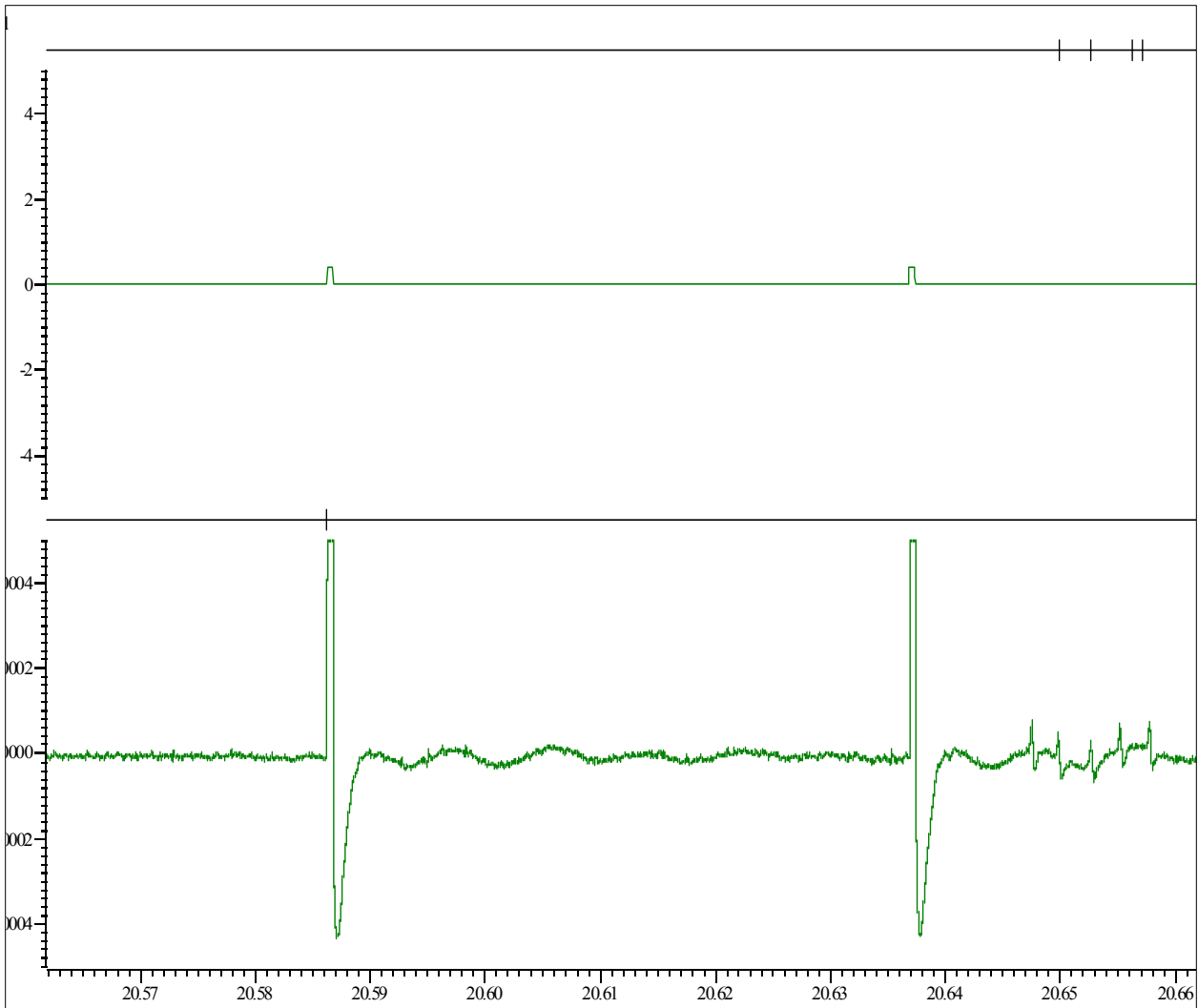


Figure 8. Upper green plot shows the current stimulus, and black line at top gives the times of action potentials

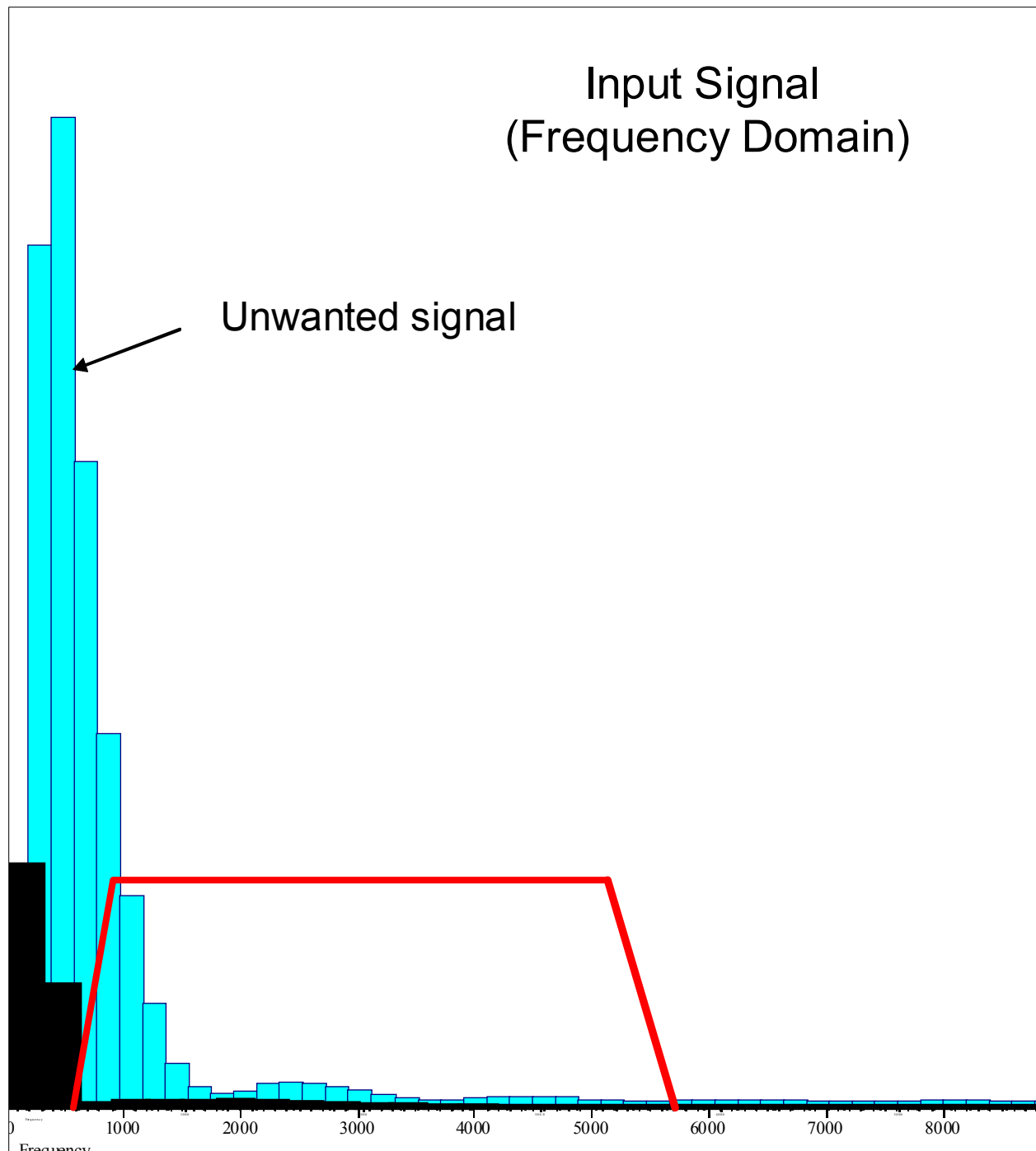


Figure 9: Frequency domain picture of stimulus artifact (blue) and neural spikes (black). The red line indicates the frequency band to be preserved after filtering.

Novel Design for Amplifier to Record Neural Spikes in the Presence of Stimulus Artifact

Our solution is to sample the input very fast and store the sampled value on a capacitor at the negative input of the front stage amplifier. We feed the input directly to the positive input of the amplifier and thus amplify the difference between the sampled and the actual input (Figure 9). If sampling is sufficiently fast, the large stimulus artifact will not saturate the amplifier. This allows for sufficient amplification to reduce the range of the subsequent analog-to-digital converter from 17 bites to 8 bits or less. What makes this solution desirable are its simplicity of implementation, compact area and minimal reliance on *a priori* information about the stimulating current

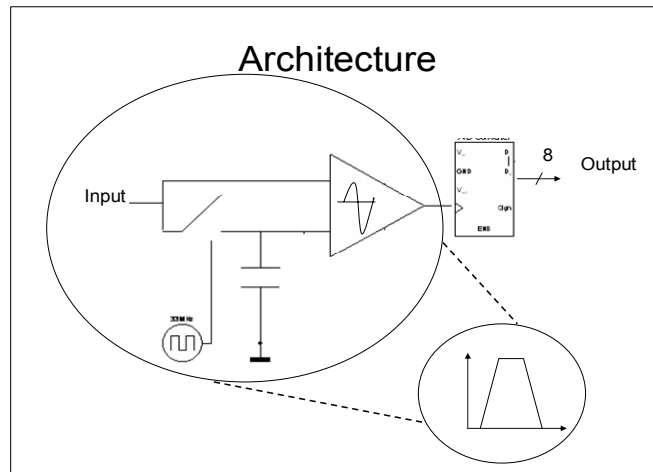


Figure 10: Input Stage architecture and its conceptual function in frequency domain modeled as a filter. The structure reduces the large stimulus artifact while preserving the small neural spike signal.

The architecture acts effectively as a high pass filter which filters specific frequencies of the stimulus artifact that are not of importance for the spikes. As was shown in Figure 9, the largest frequency components of the frequency spectrum of the unwanted stimulus artifact lie in the band between DC and 500Hz. Since this information is not important in terms of the spikes it can be filtered which reduces the dynamic range requirement for the input amplifier and maintains the integrity of the desired spike signal. An important assumption for the above solution is that the stimulus artifact is slower than the sampling frequency. For that purpose the input stage has to be a band-pass filter to eliminate fast large changes in the input which will saturate the front-end amplifier. The band-pass design uses a limiter circuit which for small inputs amplifies the signal but for very rapid and large input changes sets the amplifier output to 0. This prevents the amplification path from saturating and losing the neural signal during the recovery time from saturation by the amplifiers.

In addition the input stage has a means for reducing $1/f$ noise at the amplifier stage. Chopper modulation appears to be the best approach in terms of power and area consumption since the alternative method (correlated double sampling) requires large capacitors and is not area efficient. The large input impedance of the recording electrodes makes the chopping very hard because switching at the input introduces charge injection currents and clock feed-through, which are directly coupled to the input. Our design incorporates the chopper in the preamplifier stage itself, so that the input is decoupled from the switching waveforms. Operation of the entire system is demonstrated in the simulation in Figure 11.

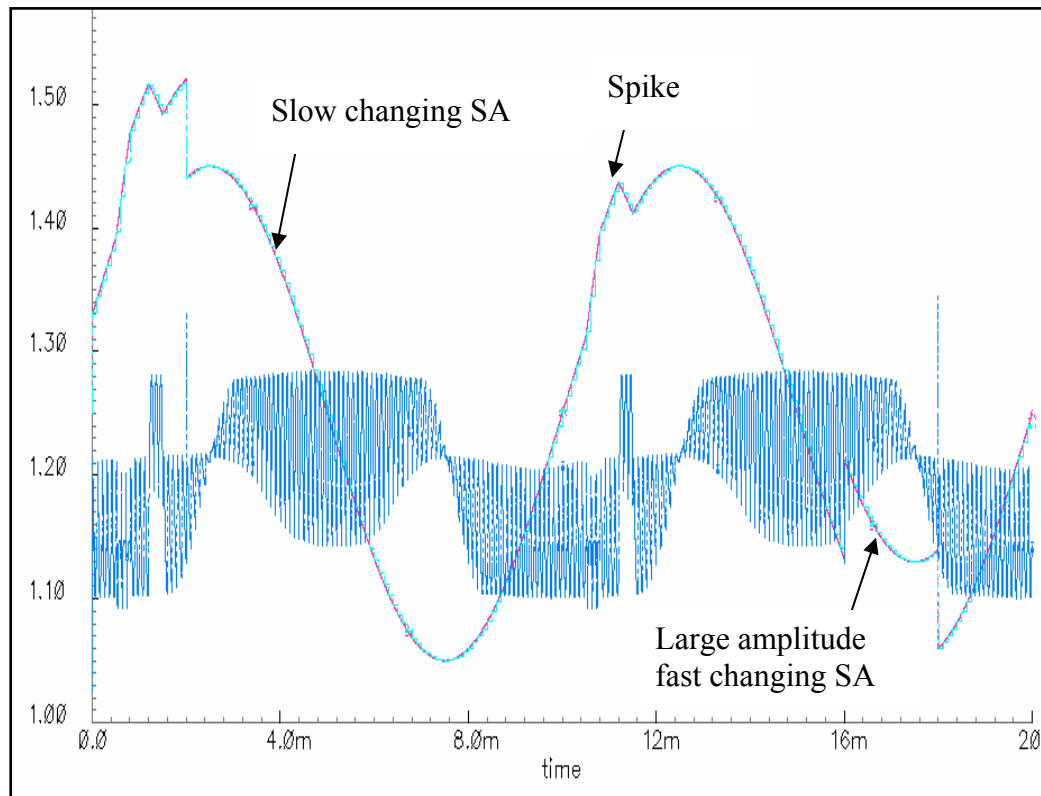


Figure 11: Limiter circuit simulation. The input is a sine-wave representing the slowly varying components of the stimulus artifact, with a superimposed large square-wave riding on top representing the large fast changing stimulus artifact components. A smaller amplitude square-wave is superimposed on the previous two to model the desired neural spike. The output is sampled and subtracted from itself and then chopped. At the negative peaks of the sine-wave the output is the same even though the input at one of them contains a large square-wave superimposed. This demonstrates the operation of the limiter. It ignores large swift changes in the input while it responds to the smaller amplitude square-wave representing the neural spike.

Prototype Integrated Circuit Development

Thus far an amplification path for a single channel has been designed in 0.18 μ m CMOS. Frequency division multiplexing has been investigated since frequency shifting is already present in the amplification path for noise reduction.

Publications

Journal Articles and Patents

Published

R. Hornig, T. Laube, P. Walter, M. Velikay-Parel, N. Bornfeld, M. Feucht, H. Akguel, G. Rossler, N. Alteheld, D.L. Notarp, J. Wyatt, G. Richard, "A Method and Technical Equipment for an Acute Human Trial to Evaluate Retinal Implant Technology", *Journal of Neural Engineering*, vol. 2, (2005), pp. 129ff

J.L. Wyatt, Jr., J. Rizzo, L. Theogarajan, "Minimally Invasive Retinal Prosthesis" , U.S. Patent 6,976,998 B2, December 20, 2005.

Accepted for Publication

Montezuma, S., Loewenstein, J., Scholz, C., Rizzo, J., "Biocompatibility of subretinal materials in Yucatan pigs," *Investigative Ophthalmology and Visual Science*, accepted March 2006

Meeting Papers

Presented

J.L. Wyatt, J.F. Rizzo, L. Theogarajan, D.B. Shire, S.K. Kelly, M.D. Gingerich, S. Cogan, M. Markova, O. Ziv, "Engineering Development of a Prototype Wireless Subretinal Prosthesis," ARVO Lecture Abstract 1146, 2005.

J. Wyatt, J. Rizzo, "Development of a Wireless First Generation Boston Retinal Implant Subretinal Prosthesis," Proceedings of The Eye and the Chip - 2006 World Congress on Artificial Vision, Detroit, MI, June 2006.

Gingerich, M.D., D.B. Shire, J. Chen, J. Loewenstein, H.A. Shah, J. Sun, J.L. Wyatt, J.F. Rizzo, "Surgical Guides for Electrode Array Implantation into the Subretinal Space," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, 2005, abstract 1494.

Shire, D.B., M. Gingerich, J.F. Rizzo, J.L. Wyatt, "Recent Developments in Inflatable Prostheses for Epiretinal Stimulation and/or Recording," ARVO Poster Abstract, Investigative Ophthalmology and Visual Science, Ft. Lauderdale, FL, 2005, abstract 1534.

G. Swider, L. Theogarajan, W.A. Drohan, S.K. Kelly, B.M. Yomtov, J.L. Wyatt, J.F. Rizzo, "Testing and Qualification of the Boston Retinal Implant Chip," poster 3187, ARVO, 2006.

W.A. Drohan, L. Theogarajan, S.K. Kelly, J.L. Wyatt, B.M. Yomtov, J.F. Rizzo, "Development of Retinal Implant Driver Software for Retinal Implant Project," poster 3167, ARVO, 2006.

S.K. Kelly, M. Markova, L. Theogarajan, W.A. Drohan, G.W. Swider, B. Yomtov, J.L. Wyatt, J.F. Rizzo, "Development of a Telemetry System for the Boston Retinal Implant," poster 3168, The Association for Research in Vision and Ophthalmology (ARVO), 2006.

D.B. Shire, S.F. Cogan, M.D. Gingerich, J.L. Wyatt, and J.F. Rizzo, "Transparent Epiretinal Electrode Array for Chronic Recording to Study Neural Coding for Vision," Invest. Ophthalmol. Vis. Sci. 2006 47: E-Abstract 3162.

Chapter 16. The Retinal Implant Project

Published

L. Theogarajan, J. Wyatt, J. Rizzo, B. Drohan, M. Markova, S. Kelly, G. Swider, M. Raj, D. Shire, M. Gingerich, J. Loewenstein, B. Yomtov, "Minimally Invasive Retinal Prosthesis," IEEE International Solid-State Circuits Conference (ISSCC), February, 2006.

Internet Dissemination

www.BostonRetinalImplant.org