INTRAOCULAR RETINAL PROSTHESIS TEST DEVICE

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Abstract - **There is a growing interest in the development of a retinal prosthesis device based on a number of recent experiments demonstrating electrical stimulation of retinal tissue with single electrodes. An intraocular retinal prosthesis test device is currently under development at NRL/JHU. The microelectronic device has an image format of 80 x 40 unit cells interfaced to the retinal surface via an array of microwires in a glass matrix. The system architecture and technology development issues are discussed as well as the topic of biocompatibility. This test device will enable acute human experiments in an operating room environment to demonstrate a massively parallel interface between retinal tissue and a microelectronic array.**
Keywords – **Retina, prosthesis, channel glass, multiplexer**

1. INTRODUCTION

Recent advances in the fields of microelectronics, neurophysiology, and retinal surgery have progressed to the point where an implantable visual prosthesis system, based on electrical stimulation, is now considered feasible. Currently a number of research projects around the world are aimed at developing prosthetic vision systems. The device discussed in this paper addresses the technical problem of positioning a high-density electrode array against the retina to achieve high-resolution retinal stimulation and perception of image sequences in the patient.

The outermost layer of the sensory retina consists of photoreceptors; in the macular region, the photoreceptors are mostly cones (color-sensitive). The next layers of the sensory retina are the bipolar, amacrine, horizontal, and the ganglion cells. The axons of the ganglion cells form the optic nerve.

Photoreceptor loss from diseases such as retinitis pigmentosa and age-related macular degeneration are the leading causes of legal blindness. Despite near-total loss of photoreceptors, there is relative preservation of the other retinal neurons. By stimulating the remaining functional retinal layers, it may be possible to restore visual perception.

Initial experiments with intraocular stimulation, were performed by de Juan and Humayun several years ago [1]. Since that time, a number of research groups have begun the development of retinal prostheses [2,3,4,5,6,7,8]. Some groups are working toward a device that will be implanted on the *epiretinal* retinal surface while others are developing a *subretinal* implant.

Epiretinal implantation has the advantage of leaving the retina intact by placing the implant in the vitreous cavity, a naturally existing and fluid-filled space. Studies at John Hopkins University Hospital have demonstrated that this array position is biocompatible [9]. Subretinal implantation of a retinal prosthesis essentially replaces the diseased photoreceptors with a microelectronic stimulator device. However, the surgical implantation requires detaching the retina, and the location of the device may be disruptive to the health of the retina.

Section 2 gives an overview of the intraocular retinal prosthesis (IRP) concept and associated electrical stimulation of the retina. In Section 3, the development of a curved surface electrode array is discussed that is fabricated using channel glass. Efforts to design and fabricate a microelectronic multiplexer array for an IRP test device are described in Section 4.

2. INTRAOCULAR RETINAL PROSTHESIS

The basic operation of an IRP device is straightforward: visual images can be produced in the brain by electrical stimulation of retinal cells. A layer of retinal cells, such as a ganglion cell layer, can be stimulated using an adjacent microelectronic array that inputs electrical impulses. The axons of the stimulated ganglion cells then transmit the image through the optic nerve to cells in the visual cortex to create the perception of an image. This is in place of the normal photo-transduction process that occurs in a healthy retina. In a large percentage of blind patients, the photoreceptors are diseased, but the other retinal layers are still responsive to electrical stimulation [10].

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Abstract

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A number of technical issues must be addressed in designing and fabricating a retinal prosthesis device that will generate a high-resolution image. First, there is the issue of creating an electrical interface between the high-density electrode array and the curved surface of the retina. The electrode array must have a spherical, convexed shape to conform to the spherical concaved surface of the retina. The electrode array must be biocompatible and safe for permanent implantation. Second, the electrical stimulation pulse shapes and repetition rates need to be determined in general and may need to be optimized for each patient. Third, direct electrical stimulation of the ganglion cells precludes certain image processing functions that normally would have occurred in earlier layers of the retina. Therefore, image preprocessing operations may need to be performed on the image before stimulation of the retina. Fourth, supplying power to a permanent implant will need to be engineered in a manner such that there are no wires or cables through the eye wall. Fifth, because a normal retina processes image information created by the photoreceptors in a simultaneous manner, it is assumed that a prosthesis device should similarly excite retinal cells in a simultaneous manner (as opposed to a sequential raster scan like that used in video displays).

A microelectronic stimulator array is described below that addresses many of the technical issues discussed above. The current joint effort between the Naval Research Laboratory and Johns Hopkins University is aimed at developing a microelectronic IRP stimulator array that will be used in preliminary short-term tests in an operating room environment. The IRP test device will receive input images from an external camera connected via a microcable. These tests will determine requirements for a permanent IRP implant device.

The IRP test device will enable short-term human experiments (less than an hour) to study basic issues involved with interfacing a massively parallel electrode array to retinal tissue. The design combines two technologies: (1) electrode arrays fabricated from nanochannel glass (NCG) [11], and (2) infrared focal plane array (IRFPA) multiplexers [12].

NGC is a technology that uses fiber optic fabrication techniques to produce thin wafers of glass with very small channels perpendicular to the plane of the wafer [13,14]. Typical NCG wafers that will be required for retinal prosthesis devices are several millimeters in diameter and contain millions of channels, with channel diameters on the order of one micron. The channels are filled with a good electrical conductor, and one surface of the glass is ground to a spherical shape consistent with the radius of curvature of the inside of the retina. The electrical conductors on the curved surface should protrude slightly to form efficient electrodes. NCG technology will be discussed in Section 3.

For the IRP test device, a microelectronic multiplexer is required. The IRFPA community has been developing a similar multiplexer technology over the past decade. IRFPAs use microelectronic multiplexers that are fabricated at silicon foundries. The multiplexer is a two-dimensional array that reads-out the infrared images captured by a complementary detector array that converts photons into electrical charge. The charge is integrated and stored in each pixel (sometimes referred to as a unit cell) for a few milliseconds. The full image is then multiplexed off the array at frame rates compatible with commercial video. For an IRP test device, the process is essentially reversed, and the device acts as demultiplexer. That is, an image is read onto the stimulator array. Although devices discussed here for IRP will perform demultiplexing operations, they are simply referred to as multiplexers.

Figure 1 shows an IRP test device positioned against the retina as it would be in an acute human experiment performed by an ophthalmologist. The experimental procedure uses standard retinal surgical techniques in an operating room environment. It is necessary that the patient be administered local (rather than general) anesthesia so that he is conscious during the procedure.
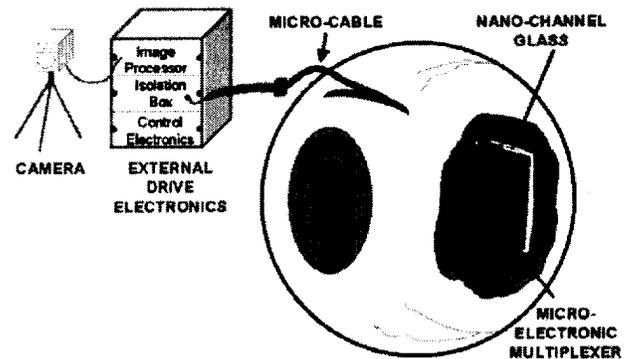

Figure 1 - An IRP test device positioned against the retina as it would be in an acute human experiment performed by an ophthalmologist. External drive electronics are needed to control the device and interface it with a standard video camera.

Figure 2 shows a side view of the fully packaged IRP test device. The NCG is hybridized to the multiplexer using indium bump bonds–again, this is similar to hybridization techniques used in IRFPAs. The image is serially input onto the multiplexer via a very narrow, flexible microcable. Note that the electrical connection to the silicon multiplexer is made so there is nothing protruding above the spherical curved envelope defined
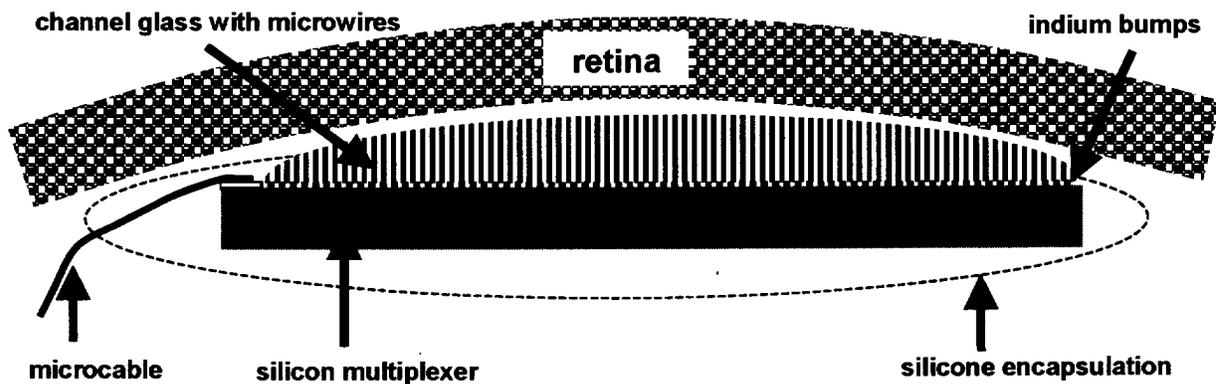
Figure 2 - Side view of the fully packaged *IRP test device*. The NCG is hybridized to the multixplexer using indium bump bonds.

by the polished NCG surface and therefore protects the retina from damage.

A critical issue for any neural prosthesis device is biocompatibility and safety. Because the duration of any tests with the IRP test device are very short (less than an hour), biocompatibility issues are primarily reduced to acute effects and need not address the more difficult chronic issues that arise with permanent implants. Note that the surface of the packaging shown in Figure 2 consists only of glass, platinum electrodes, and silicone encapsulation. However, as with any electronic medical instrumentation, a major safety issue is electrical shock hazard. The purpose of the device is to provide minimal electrical stimulation of retinal tissue using very low voltages and the smallest currents possible. During this procedure the patient must be connected to external instrumentation. To protect the patient from any electrical shock, the patient is isolated from high voltages using low voltage batteries and optocouplers to input signals.

Many questions and concerns arise when interfacing a stimulating electrode array to neural tissue. One fundamental concern is that because the retina is a thin layered structure, more than one layer may respond to electrical stimulation. Other questions involve electrode configurations, electrical currents, and pulse shapes, as well as the important issues of safety and biocompatibility.

There are well-defined relationships between the threshold current and the stimulus pulse duration required for neuronal activation [15]. As the stimulus pulse duration decreases, the threshold increases exponentially. Also, as the pulse duration increases, the threshold current approaches a minimum value Experiments were performed at Johns Hopkins University to define threshold currents for retinal electrical stimulation. One study assessed the effect of changing parameters of the stimulating electrode and the stimulus pulse by recording electrically elicited action potential responses from retinal

ganglion cells in isolated rabbit retina [16]. It was concluded that the threshold for stimulation from the ganglion side is lower then from the photoreceptor side, especially when using microelectrodes (19.05 µA versus 48.89 µA, with pulse duration of 0.5 msec). Recently, similar experiments with very small electrodes (10 µm diameter) demonstrated successful stimulations with currents as low as 0.14 – 0.29 µA[17,18].

3. MICRO-ELECTRODE ARRAY

Specific requirements for the NCG are that the channels be small enough so that many microwires can be connected to each unit cell. This provides redundancy, but more importantly helps simplify the alignment process when the electrode array is hybridized to the silicon multiplexer. If the NCG microwires were to approach the size of the multiplexer unit cells, than a one-to-one alignment would be required. This would be very problematic because of irregularities in the channel glass periodicity and the possibly of shorting nearest-neighbor cells. On the other hand, very narrow channels imply very high length-to-width aspect ratios for the channel geometry. This makes it difficult to fabricate large-area NCG samples with the proper thickness. Therefore, a reasonable design goal for the channel width is a diameter of about one micron.

Both microchannel glass and nanochannel glass are fabricated using glass-drawing procedures that involve bundled stacks of composite glass fibers. The process begins by placing an acid-etchable glass rod into an inert glass tube and drawing this pairing of dissimilar glasses at elevated temperature into a fiber of smaller diameter. Several thousand of these fibers are then cut and stacked in a hexagonal-close-packed arrangement, yielding a hexagonal-shaped bundle. This bundle is subsequently drawn at elevated · temperature, fusing the individual composite fibers together while reducing the overall bundle size. At this stage, the fibers are hexagonal shaped
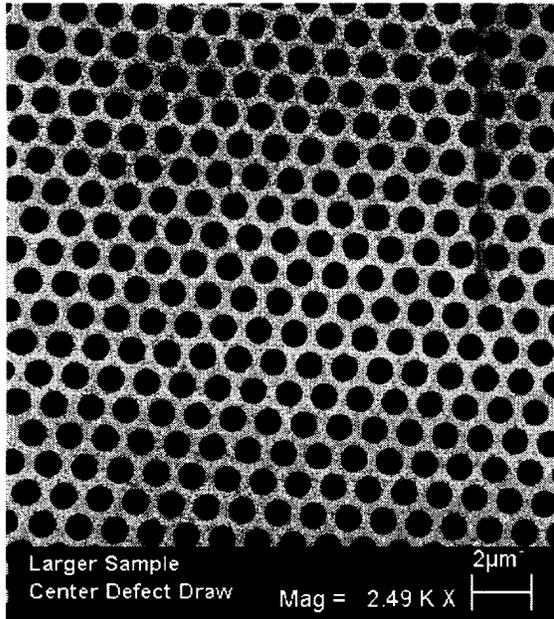
Figure 3 - SEM micrograph of nanochannel glass having 0.8 micron diameter channels.

and fusing the bundle together at elevated temperature.

Similarly, nanochannel glass may be fabricated by stacking the hexagonal shaped fibers into a new bundle which is then drawn at an elevated temperature, thereby fusing the individual fibers together and reducing the overall size. In this manner, submicron channel diameters and extremely high channel densities can be achieved. After the last glass draw, the boules are wafered, polished and then etched to remove the acid etchable glass. In this way, a glass with extremely uniform, parallel, hollow channels is obtained. An SEM micrograph of nanochannel glass having channel diameter of 0.8 microns is shown in Figure 3.The NCG channels must be filled with a high conductivity material to create microwires. The microwires can be fabricated using electrodeposition or infusion of molten metal under pressure. After the channels have been filled with a conductive material and the continuity of the microwires has been confirmed, one side of the glass must be curved to create a spherical surface. Grinding and polishing techniques similar to those used in lens fabrication can be applied to the NCG pieces. The radius of curvature is nominally 12.7 mm to provide a conformal fit against the inside of the retina. This is critically important as it allows positioning of the high-density electrodes in direct contact with the retinal tissue. The polishing process will create slightly recessed microwires with respect to the curved NCG surface. This is because the metal is softer than the glass. Therefore further processing is necessary to create
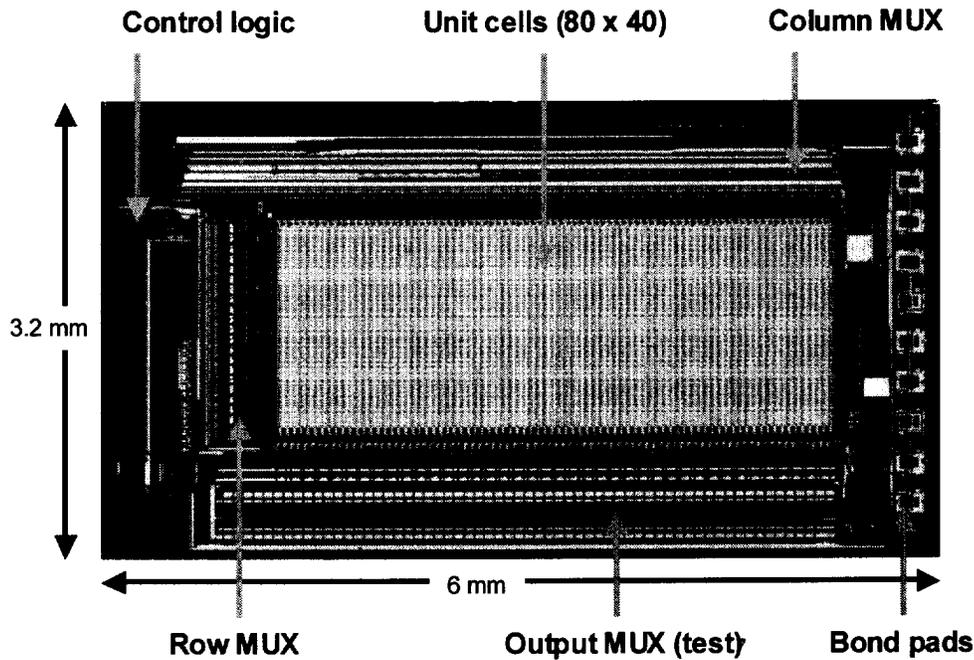
and contain a fine structure of several thousand micron-sized (typically 5 to 10 micron diameter) acid etchable glass fibers in a hexagonal-close-packed pattern. Standard microchannel plate glass is obtained at this point by bundling these fibers together in a twelve-sided bundle

Figure 4 – Layout of microelectronic *de-multiplexer* that accepts a standard RS-170 video input and routes signals to the individual unit cells which in turn drive simultaneous current pulses into retinal tissue at a rate of 60 frames a second. Output MUX is for diagnostic test and performance monitoring.

electrodes that protrude slightly above the curved surface. This can be accomplished by applying a chemical etch to the surface that removes a few microns of glass.

The microwires can be hybridised directly to indium bumps deposited on the multiplexer if they are formed to protrude slightly from the flat-side of the NCG. Getting the microwires to protrude could again be accomplished by chemical etching like that described above for forming protruding electrodes on the curved side of the NCG.

Currently, the electrode arrays that are being fabricated at NRL by electrodeposition of metals within microchannel glass and nanochannel glass templates. The total number of electrodes in an array of dimensions 2 mm x 5 mm can range up to several million. It should be noted that the total number of electrically addressable pixels (or unit cells) on the silicon multiplexer array is 3200. Therefore, a considerable redundancy is achieved in the number of electrodes associated with each pixel.

4. MICROELECTRONIC MULTIPLEXER DESIGN

The silicon multiplexer discussed previously in Section 2 performs several operations in a sequential order. During the first step, an image frame is read onto the multiplexer, pixel-by-pixel, to each unit cell. Row-by-row, each unit cell samples the analog video input and stores the pixel value as charge on a MOS capacitor. A full field is completed every 60th of a second in a manner compatible with the RS-170 television format (30 frames per second consisting of two fields per frame); this allows the use of the test prosthesis with standard video equipment.

Figure 4 shows the multiplexer jointly developed by NRL and Raytheon RIO Corporation. The control logic sector is of major importance because it generates the switching pulses that route image data into the unit cells. Without this on-chip digital electronics sector, a dozen or more clocks would need to be input to the device. That would make the cable through the eye wall much more cumbersome and susceptible to electrical crosstalk.

After all the unit cells have been loaded with the pixel values for the current frame, the next step is to send a biphasic pulse to each unit cell, which in turn is modulated in proportion to the pixel value stored in each unit cell. The biphasic pulse flows from an external source, through each unit cell, thus stimulating retinal neurons in a simultaneous manner. This is an important feature of the design because it is a completely synchronized action analogous to photons stimulating photoreceptors in a normal retina. Finally, the electrodes are all connected to ground to prevent any possible charge buildup at the electrode-neuron interface.

There are several important considerations in designing a device that performs all these operations

successfully. First, the multiplexer operation should be designed with many of the requirements that exist for imaging arrays, for example, good uniformity, low noise, and high dynamic range. Of course, the retinal prosthesis test device moves image data in the opposite direction than a conventional imaging multiplexer, that is, the image moves onto the device rather than off the device, but otherwise the specifications are analogous.

Figure 5 shows a simplified circuit design for a unit cell. An important feature is that each unit cell stores individual pixel values and then use them to modulate the biphasic pulse that is input to the retinal tissue through the NCG. Note that the biphasic pulse and the image data are both generated off-chip. This allows for greater flexibility during human testing as any image sequence can be input and combined with any shape of biphasic pulse. The switch at the bottom of Figure 5 provides the capability to connect the retinal tissue to ground to avoid any possibility of charge build-up.
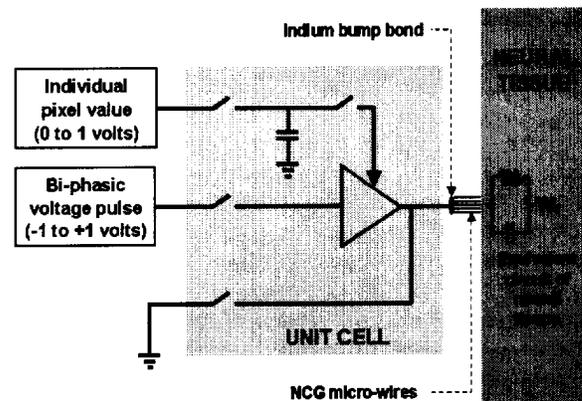

Figure 5 – Simplified circuitry of the unit cell in the *IRP test device* showing the external inputs from off-chip. The pixel values are acquired from a camera (or any other video system that generates RS-170 signals).

As mentioned above, the multiplexer array can be designed to sample the multiplexed input signal in a manner compatible with the RS-170 format. This allows the IRP test device to be interfaced directly with any standard video camera. This includes the use of a personal computer that stores digital imagery and can display sequential fields at a 60 Hz rate (RS-170 interlaces two fields per frame at a rate of 30 frames per second).

An external set of drive electronics control of the multiplexer array using precisely timed pulses in a manner similar to that used in typical imaging arrays. A sync pulse generator is used to synchronize the RS-170 signal with the clocking pulses.

5. SUMMARY

The hope of restoring vision to the blind is now believed to be a real possibility using neural prosthetics.

The IRP test device described above is an important step toward demonstrating a massively parallel interface between a microelectronic array and retinal tissue. However, many technical problems remain and many engineering issues must be resolved before complete clinical success is achieved. Not the least of these problems will be solving the issues of biocompatibility and the reliability of a device that will be implanted and expected to function without degradation for decades. Ultimately, the true measure of success will be the acceptance of this approach by the blind community. Hopefully this success will parallel that of the cochlear implant that, although initially slow, continues to grow exponentially each year and is now a fully commercialized medical product.

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REFERENCES

[1] Humayun, M. and Propst, R., de Juan, E. J., et al, "Bipolar surface electrical stimulation of the vertebrate retina," *Arch. Ophthalmol.*, vol. 112, pp. 110-116, 1994.

[2] Zrenner, E., Stett, A., Weiss, S., et al., "Can subretinal microphotodiodes successfully replace degenerated photoreceptors?" *Vision Res.*, vol. 39, pp. 2555-2567, 1999.

[3] Humayun, M. S., de Juan, E. J, Weiland, J.D., et al., "Pattern electrical stimulation of the human retina," *Vision Res.*, vol. 39, pp. 2569-2576, 1999.

[4] Chow, A. Y. and Peachey, N. S., "The subretinal microphotodiode array retinal prosthesis," *Ophthalmic Res.*, vol. 30, pp. 195-198, 1998.

[5] Eckmiller, R., "Learning retina implants with epiretinal contacts," *Ophthalmic Res.*, vol. 29, pp. 281-289, 1997.

[6] Wyatt, J. and Rizzo, J. F., "Ocular implants for the blind," *IEEE Spectrum*, vol. 112, pp. 47-53, 1996.

[7] Veraart, C., Raftopoulos, C., Mortimer, J. T., et al., "Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode," *Brain Res.*, vol. 813, pp. 181-186, 1998.

[8] Yagi, T. and Hayashida, Y., "Implantation of the artificial retina." Nippon Rinsho, vol. 57, pp. 1208-1215, 1999.

[9] Majji, A. B, Humayun, M. S, Weiland, J. D., et al., "Long-term histological and electrophysiological results of an inactive epiretinal electrode array implantation in dog," *Invest. Ophthalmol. Vis. Sci.*, vol. 40, pp. 2073-2081, 1999.

[10] de Juan, E., Humayun, M. S., Hatchell, D., and Wilson, D., "Histopathology of experimental retinal neovascularization," *Invest. Ophthamol.*, vol. 30, pp. 1495, 1989.

[11] Tonucci, R. J., Justus, B. L., Campillo, A. J., and Ford, C. E., "Nanochannel array glass," *Science* vol. 258, pp.783-785, 1992.

[12] Scribner, D. A., Kruer, M. R., and Killiany, J. M., "Infrared focal plane array technology," *Proc. IEEE*, vol. 79, pp. 65-85, 1991.

[13] Tonucci, R.J. and Justus, B.L., "Nanocchannel Glass Matrix Used in Making Mesoscopic Structures," U.S. Patent 5,264,722, issued November 1993.

[14] Tonucci, R.J. and Justus, B.L., "Nanochannel Filter," U.S. Patent 5,234,594, issued August 1993.

[15] West, D. C. and, Wolstencroft, J. H., "Strength-duration characteristics of myelinated and non-myelinated bulbospinal axons in the cat spinal cord," *J. Physiol. (London)*, vol. 337, pp. 37-50, 1983.

[16] Shyu, J., Maia, M., Weiland, J., et al., "Electrical Stimulation of Isolated Rabbit Retina," Biomedical Engineering Society Annual Meeting, Seattle, WA, USA, 2000.

[17] Grumet, A. E., Rizzo, J. F., and Wyatt, J. L., "Ten Micron Diameter Electrodes Directly Stimulate Rabbit Retinal Ganglion Cell Axons," ARVO abstracts, Ft. Lauderdale, FL, p. 3883, 1999.

[18] Grumet, A. E., Rizzo, J. F., and Wyatt, J., "In-vitro electrical stimulation of human retinal ganglion cell axons," ARVO abstracts, Ft. Lauderdale, FL, p. 50, 2000.