Microelectronic Array for Stimulation of Retinal Tissue

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PROJECT BACKGROUND AND GOALS

The development of a high-resolution retinal prosthesis device at the Naval Research Laboratory (NRL) was first discussed in the late 1990s. At that time, NRL researchers and Office of Naval Research (ONR) Science Officers were studying the topic: "Image Processing: What Can We Learn from the Retina?" It had long been recognized that the retina must perform remarkable image processing functions, yet neuroscientists had only a limited understanding of the systemic mechanisms. ONR felt that studying retinal mechanisms could provide valuable inspiration for new algorithms and low-power analog designs for microelectronic circuitry in future electro-optical imaging arrays.

Although "smart focal plane arrays" had been of great interest to the electro-optical community, traditional digital image processing was far too power-hungry to integrate into a focal plane array. Analog ("retina-like") processing might provide new methods that would allow computationally intensive algorithms to be performed in parallel while dissipating only small amounts of power.

ONR had also been discussing related topics with the Wilmer Ophthalmological Institute of Johns Hopkins University (JHU). The JHU team was not only interested in retinal processing mechanisms, but was performing some interesting experiments that were aimed at demonstrating the feasibility of a retinal prosthesis—namely, electrically stimulating retinal cells and analyzing the perceived effects in blind human subjects.

It was this overlapping mutual interest in the retina that led NRL researchers to propose the use of advanced DoD technologies for a revolutionary new neural-electronic interface for both a retinal prosthesis and for advanced retinal studies.

At the same time, a new DARPA program was soliciting proposals for the development and demonstration of innovative tissue-based biosensors that would be a key component in DARPA's programs in Biological Warfare Defense. Of particular interest was the capability to rapidly detect and predict physiological consequences of biological and chemical agents, both known and unknown. DARPA foresaw the need for new techniques to create an effective and massively parallel interface between microelectronic arrays and neural cells.

In response to this DARPA program, NRL proposed to design and fabricate a miniaturized, high-resolution human retinal stimulator device to be used in conjunction with the Johns Hopkins University program. The device would create a neural-electronic interface between a high-resolution array of 3,200 microelectrodes and a retinal surface. The proposal was unique because a microelectronic interface to neural tissue with 3,200 independent electrodes was unprecedented. It supported the DARPA program because it would provide detailed information about microelectronic interfaces at a cellular level.

Development of a Test Device for Acute Experiment

The development of an implantable retinal prosthesis for chronic use is a complex undertaking. Such a device would require wireless operation; it must meet stringent biocompatibility requirements; and it must have a lifetime of several decades. A logical first step is to make a test device that can be used in very short, acute experiments to prove the feasibility of a high-resolution device. In the early 1990s, the Johns Hopkins group performed human experiments with a single electrode used to electrically stimulate the retina. Since that time, a number of research groups have begun to develop technologies that support retinal prostheses.

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A review article in the journal *Science* details this field of research.[1] Currently most conceptual designs for retinal prostheses are attempting to provide only the most rudimentary vision. Furthermore, these technologies are not scalable to higher resolution. The NRL retinal device seeks to remedy these problems.

The remainder of this paper describes the program at NRL for designing, fabricating, and testing a high-density electrode array that would be suitable for acute tests with human subjects. This will lead to clinical tests to begin in 2005 by a surgical team in an operating room environment. The experiment would last approximately one hour. The highly trained patient would be conscious and receive high-resolution, intraocular retinal stimulation in the form of a series of image sequences and describe his or her perceptions.

Figure 1 shows the NRL test device as it will be positioned against the retina during the surgical experiment. Note that a small cable passes through an incision in the sclera, allowing a direct means of powering the device and inputting image data. Figure 2 shows the device architecture and the corresponding retinal anatomy with regard to the device placement. Note that the outermost layer of the retina consists of photoreceptors. Proceeding from the photoreceptors inward toward the center of the eye, the layers of the sensory retina are the bipolar, amacrine, horizontal, and the ganglion cells. The axons of the ganglion cells form a radial pattern across the retina and converge to form the optic nerve. Photoreceptor loss from diseases such as retinitis pigmentosa and age-related macular degeneration are the leading causes of blindness in the developing world, affecting approximately 30 million people. There are no known restorative therapies. Nevertheless, even in advanced stages of these degenerative diseases, the inner retinal layers remain viable for long periods of time. By stimulating these remaining functional retinal layers, it may be possible to restore visual perception.

The basic operation of a retinal prosthesis device is straightforward in theory. Visual images can be produced in the brain by electrical stimulation of retinal cells (which substitutes for optical stimulation) so as to provide a one-to-one mapping to areas in the visual cortex. 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.[2]

Advanced DoD Technologies for Neural-Electronic Interfaces

To meet the above-mentioned specifications, the NRL program leveraged advanced DoD technologies by (1) modifying infrared focal plane array (IRFPA) microelectronic multiplexer technology and (2) creating microwire glass electrode arrays using microchannel plate glass as the starting material. Microchannel plate glass is used in image intensifier tubes like those in night vision goggles. It is produced by a unique process that involves bundling optical fibers to produce thin wafers of glass (with all the hollow channels extending straight through the glass wafer). Microchannel sizes are typically 5 μm diameters, and the density of the microchannels is approximately 20,000 per square millimeter. At NRL, the hollow channels are filled by electroplating, which creates microwires. Then, one surface of the glass is ground and polished to a spherical shape consistent with the radius of curvature of the inside of the retina.

A primary function of the device is to multiplex image data from the incoming analog video to the individual unit cells. The IRFPA community has been developing similar integrated circuits over the past 15 years. Microwire glass 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. The electrical connection to the silicon multiplexer is made such that nothing is protruding above the spherical curved envelope defined by the polished microwire glass surface and, therefore, protects the retina from damage.

MICROELECTRONIC MULTIPLEXER

The multiplexer capability is of major importance because it allows the operation of all 3,200 unit cells with only 10 leads connected to the outside world. Directly connecting individual leads to all 3,200 unit cells would make for a very thick cable and make it highly impractical to route the image data through the eye wall. A proposed future version of the device could be wireless.

Microelectronic Multiplexer Description and Layout

The floor plan of the multiplexer is shown in Fig. 3(a). The NRL device was fabricated using a 1.2 μm design-rule process. The core area of the multiplexer

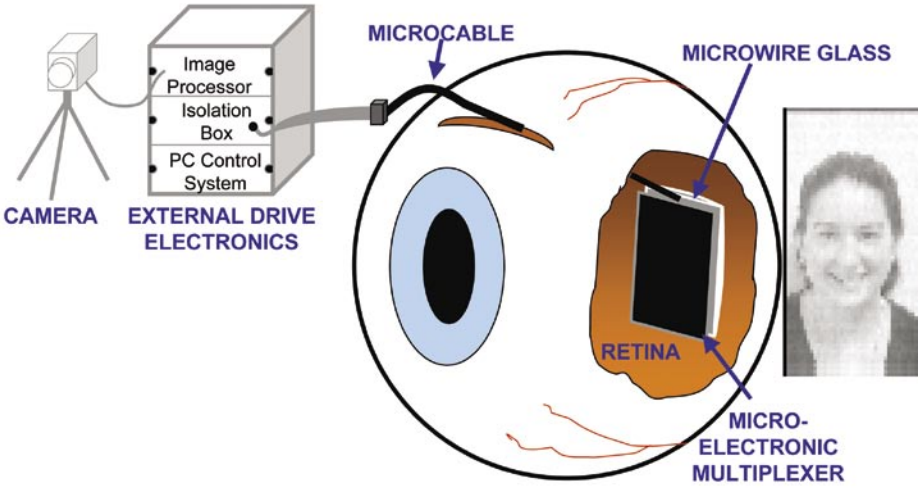

FIGURE 1
Retinal prosthesis test system, illustrating the device positioned against the retina during a one-hour surgical experiment. To provide basic visual function that is sufficient to treat common types of blindness (enough pixels for facial recognition or to read text), an extremely thin microcable passes through an incision in the eye wall, allowing a direct means of powering the device and inputting image data. The image to the right represents the image quality achievable with the 80 x 40 device. A future retinal prosthesis system, now in the planning stage, would be wireless – no microcable required – and backside illuminated.

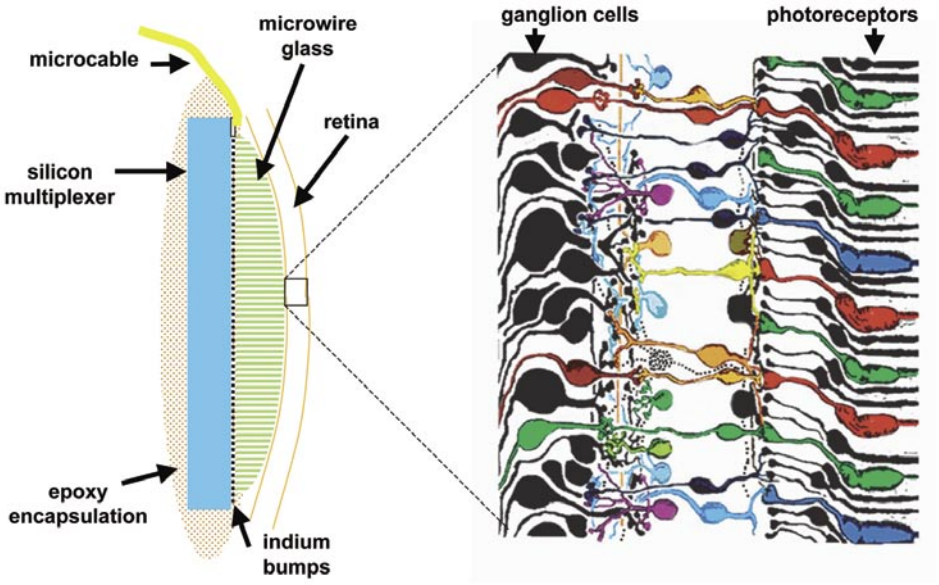

FIGURE 2
Device architecture and the corresponding retinal anatomy with regard to device placement. Note that the outermost layer of the retina consists of photoreceptors and the ends of the microwire glass are positioned in close proximity to the ganglion cell layer of the retina.

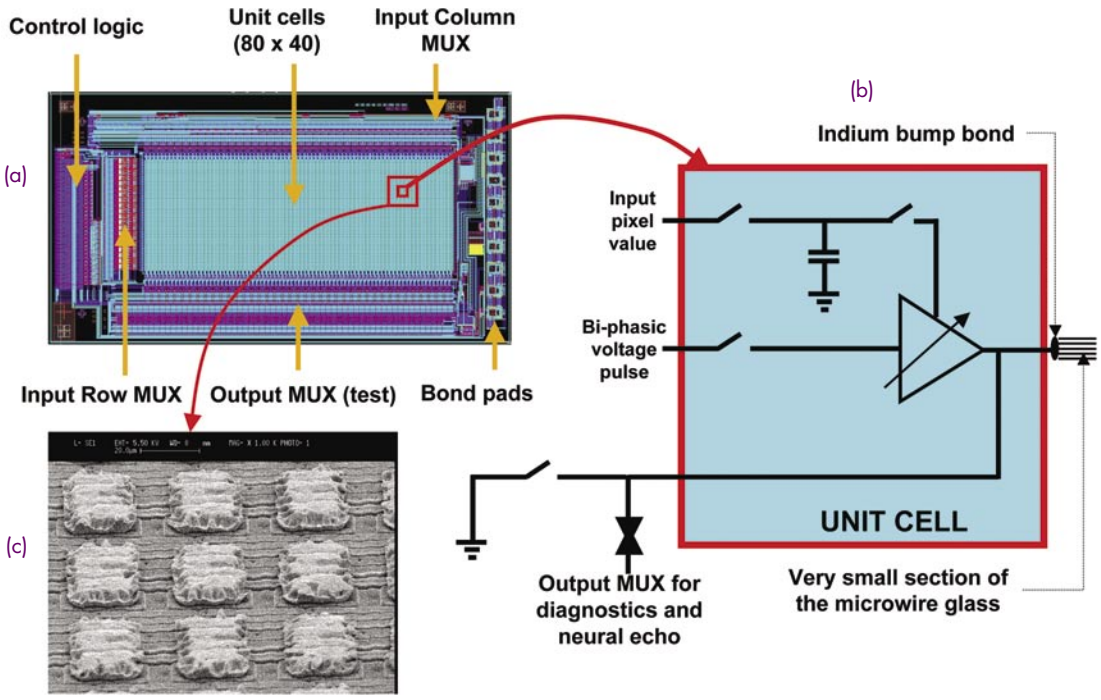

FIGURE 3
The microelectronic multiplexer floor plan is shown in (a) and a simplified schematic of the electronics in each unit cell (pixel) is shown in (b). Each unit cell has its own charge storage capacitor and a transconductance amplifier. The storage capacitors control the brightness of all 3,200 pixels within each frame. In (c), a scanning electron microscope (SEM) image of nine indium "bumps" is shown. There is one indium bump for each unit cell. Microwires on the flat side of the microwire glass will be pushed into all the bumps, connecting approximately 20 microwires to the output of each transconductance amplifier in the array. The opposite ends of those microwires will become the microelectrodes that send electrical stimulation into the retina.

is the 2D array of 80 by 40 unit cells that stimulates adjacent retinal tissue. Each unit cell is 50 by 36 μm. Although the device discussed here for use in retinal prostheses will perform demultiplexing operations, for simplicity, it will be referred to as a multiplexer.

Each unit cell has a charge storage capacitor and a transconductance amplifier as shown in Fig. 3(a). The multiplexer performs a number of important functions that are defined by its internal digital logic. The basic operation involves three steps that are performed in a sequential order and then continuously repeated at rates of up to 60 frames per second (fps). During the first step, an image frame is loaded pixel-by-pixel into corresponding unit cells. Each unit cell samples the input analog video in a raster scan format and stores the pixel value as electronic charge on an integrated circuit capacitor. A full field image can be synchronized with the RS-170 television format (30 fps consisting of two fields per frame); this allows the use of the multiplexer with standard video equipment. If standard video speeds are not required, then the frame rate can be arbitrarily changed. However, the input image will need to be timed accordingly and the device will no longer be RS-170 compatible. After all the unit cells have been loaded with the pixel values for the current frame, the second step is to send a biphasic pulse to the transconductance amplifier in each unit cell, which in turn is modulated in proportion to the pixel value stored in each unit cell.

An important feature of the multiplexer is that each unit cell stores individual pixel values and then uses them to modulate the biphasic pulse that is input to the retinal tissue through the microwire glass. 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 design also includes an output multiplexer as indicated in Fig. 3(a). Its purpose is for diagnostic testing and performance monitoring during experiments. Although actual stimulation current being driven into retinal tissue will be closely monitored, an image displayed from the output multiplexer is very useful for verifying proper operation. During testing it

allows the system operator to essentially view the same image that the patient "sees." In fact, it is possible to perform a type of extracellular recording by operating the multiplexer during quiescent periods between frames to monitor "neural echoes," the firing of retinal neurons in response to stimuli.

Indium Bump Deposition

After the multiplexers are fabricated at the silicon foundry, indium bumps are deposited to provide an electrical interconnection between the multiplexer and the microwire glass. A scanning electron microscope (SEM) image of a few indium bumps is shown in Fig. 3(c). Each indium bump is 30 by 20 μm in area and approximately 6 μm in height. The indium bump deposition is achieved by evaporation of indium into the openings of a photoresist layer on the multiplexer and then lifting off the photoresist.

MICROWIRE GLASS ELECTRODE ARRAY

Template

Production of microwire glass begins with microchannel plate glass, which serves as a kind of template in which microwires are formed. Microchannel plate glass is used in image intensifier tubes like those in night vision goggles. An SEM image of the front surface of a microchannel glass plate is shown in Fig. 4(a); these empty microchannels extend through the entire thickness of the glass plate. Microchannel plate glass has approximately two million microchannels per square centimeter!

Specific requirements for microwire glass are that the microwires be small enough so that 20 or more microwires can be connected to each unit cell or pixel. This provides redundancy as well as greatly simplifying the alignment process when the electrode array is joined ("hybridized") to the silicon multiplexer.

Three types of commercially available microchannel plates have been tested: borosilicate (similar to pyrex), soda-lime (similar to window glass), and lead glass (similar to crystal wine glasses). Tests on these candidate glasses have shown that nerve cells can be cultured on the borosilicate and soda lime glasses, but they do not survive long on the leaded glass. Susceptibility of the glass to cracking (during electroplating, polishing, or saw-cutting) is also a very important consideration. Resistance of the glass and metal to etching or leaching during extended immersion in saline solution is critical.

Microwire Formation

The hollow microchannels are filled with a metal to create a high-density array of microwires. Microwire glass is fabricated at NRL by electroplating nickel through the entire thickness of the microchannel plate glass, as shown in Fig. 4(b). The actual plating process involves current flowing through the microchannels to the backside contact. This forces the metal deposition to take place only in the microchannels, filling the microchannels with nickel and forming the microwires.

Completely electroplating metal through a microchannel plate with a thickness of 1 millimeter can take considerable time—generally one week. To expedite the processing, multiple plating baths were configured that could be operated simultaneously, but independently of each other. Each plating bath contained an 800 ml glass beaker, and up to six of these beakers were placed on a sealed 15-position stirring plate submerged in an isothermal tank. Nickel plating was performed at a 39 °C bath temperature. The plating solution in each beaker was continually stirred via magnetic bar. Bath control based on a reference electrode potential is performed by a potentiostat programmed in LabVIEW software, which also performed related data logging tasks.

Considering the huge number of microchannels in a piece of microchannel plate, nickel plating in the microchannels generally progressed with remarkable uniformity under the right conditions. When the plating was halted about halfway through the microchannel plate, cleaving the microchannel plate revealed solid microwires of nearly the same length in essentially every microchannel.

Shaping and Finishing the Microwire Glass

The resulting composite material, "microwire glass," is then cut very precisely to a size slightly larger than the central core area of the multiplexer IC chip, which contains the 80 by 40 unit cells or pixels. The core area (where electrical stimulation occurs) is 1.5 mm by 4 mm, and the microwire glass is cut to a size of 2 mm by 4.5 mm to ensure coverage of the pixel array.

Next, one side is ground and polished to obtain a smooth, curved surface that conforms to the curvature of the retina inside the eye. The microwire glass sample is polished with a series of CeO grits down to 0.5 μm. After the microwire glass sample has been sufficiently curve-polished, it is demounted and cleaned, and the

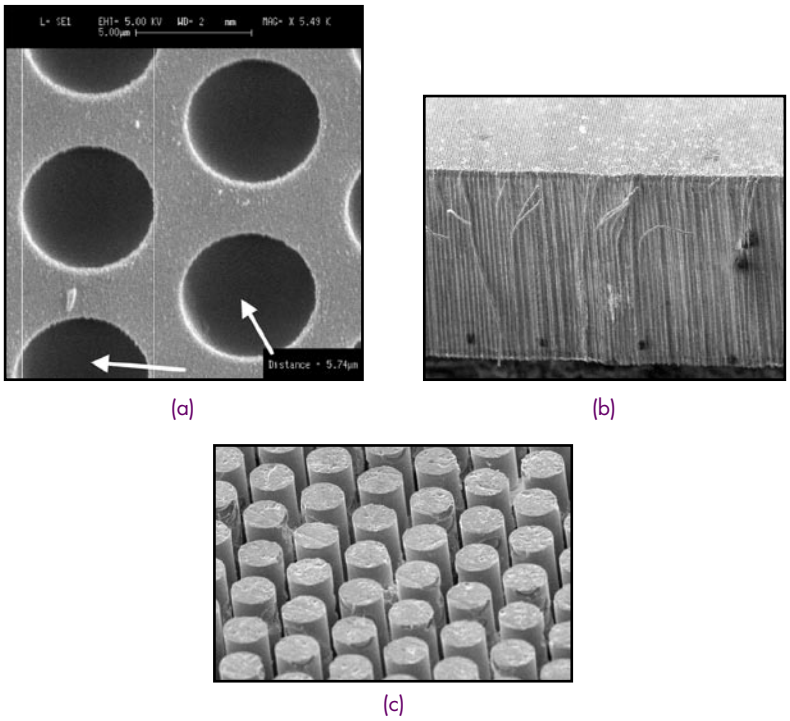

FIGURE 4
Various stages of microwire glass fabrication: (a) an SEM of the microchannel plate starting material — typical channel diameters are 5 μm with center-to-center spacings of 8 μm; (b) SEM of a cleaved edge of a nickel-filled sample — channel lengths can be plated up to one millimeter; (c) SEM view of top surface showing microwires protruding from the glass after etch-back.

curvature is checked. The radius of curvature is nominally 12.7 mm to provide a conformal fit against the inside of the retina. This allows positioning of all the microwire tips in very close proximity to the retinal tissue, minimizing the power needed to achieve retinal stimulation and also maximizing spatial resolution. The other side of the microwire glass is left flat for connection to the flat silicon multiplexer.

The entire piece of microwire glass is then placed in a hydrofluoric (HF) acid solution to chemically etch-back the glass (5 to 30 μm of glass are typically removed). This creates protruding microwires on both the curved and flat sides as shown in Fig. 4(c).

Finally, the protruding microwires on the curved side are clad with a thin layer of gold using another electroplating process. Those protruding gold-clad tips of the microwires, on the curved surface, form the microelectrode array.

DEVICE ASSEMBLY AND ENCAPSULATION

The novel design of the NRL stimulator required a number of new device miniaturization and integration methods. Assembling a complete device, like that shown in Fig. 2, involves a sequence of steps as shown in Fig. 5. First, the microwire glass piece is hybridized to the microelectronic multiplexer. Second, the microelectronic multiplexer is directly connected to a polyimide microcable via a novel ribbon bonding method. Third, the device is encapsulated with a biocompatible epoxy.

Hybridization of Microwire Glass to the Multiplexer

Hybridizing the microwire glass to the multiplexer is accomplished by pressing the microwire glass onto the indium bumps. The difficulty arises in that the top surface of the microwire glass is curved and the bottom surface that mates with the chip is flat. The flat bottom surface must maintain parallelism with the chip surface. The microwire glass is somewhat fragile, so compression must be uniform across the curved surface.

Considering the high pressure required to hybridize the two pieces, we have designed and constructed a hydraulic system that produces uniform and adjustable compression over the curved surface of the glass while also keeping accurate alignment of the two components being hybridized.

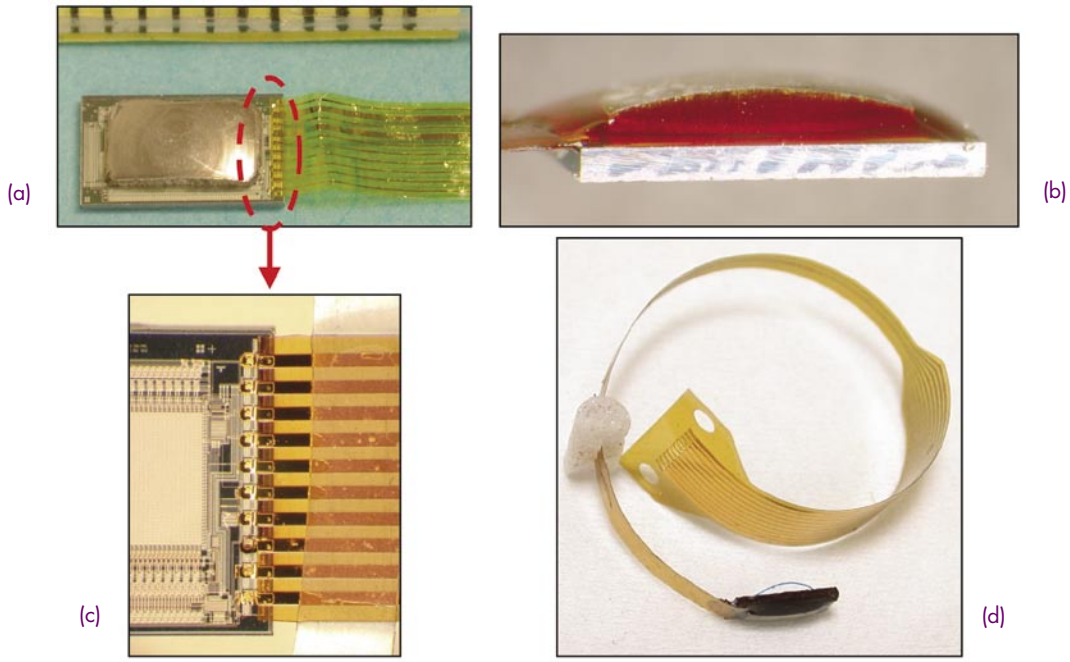

FIGURE 5
A number of steps are required to complete a fully assembled device: (a), the microwire glass piece is hybridized to the microelectronic multiplexer and the polyimide microcable is ultrasonically bonded to the 10 electrical bond pads as shown in (b). The device is then encapsulated with a biocompatible epoxy that also wicks between the microwire glass and multiplexer (c). A fully assembled device is shown in (d).

Pressures of up to 1,000 psi can be applied uniformly across the surface of the glass with the system. This presses the microwires (on the flat side of the microwire glass) into the indium bumps on the multiplexer. The microwires on the curved side of the microwire glass are held by a highly flexible latex layer, so no distortion or bending of the microwires will occur during hybridization.

Ultrasonic Bonding of Microcables to the Multiplexer

The microcable serves as the connection to the multiplexer and passes through the sclera as shown in Fig. 1. The microcable must be both flexible and tough. There are 10 electrical lines within the microcable to carry power and signals to and from the multiplexer chip. The microcable is a laminate made of two outer layers of polyimide with gold electrical traces between them. The total thickness of the microcable is 25 μm.

The microcable is fabricated such that bare gold traces extend beyond the polyimide. These short gold "ribbons" can be ultrasonically bonded directly to the bond pads on the multiplexer as shown in Fig. 5(b). After ultrasonic bonding, a small amount of the nonconducting epoxy is added to reinforce the connection. At the other end, the microcable is clamped to the minicable with a small printed circuit board that becomes a custom part of a commercially available connector.

Encapsulation and Plasma Etching

To protect the microelectronic multiplexer from the damaging saline environment of the eye, a Class IV biocompatible epoxy (Epotek™ 353ND) is used as a sealant. In addition to being safe for implantation, the 353ND nonconducting epoxy has a very low viscosity (25,000 to 35,000 cPs, at 23 °C). The low viscosity enables the epoxy to wick between the microwire glass and the multiplexer as well as in the ~3 μm spaces between the microwires. This ensures a good seal to exclude saline from contacting the multiplexer as well as stabilize the device. The low viscosity requires a mold to form the epoxy around the device. The Teflon™ mold resists adhering to the epoxy after the 30-min epoxy cure at 125 °C.

DEVICE OPERATION AND LABORATORY TESTING

The device is operated by a set of external electronics consisting of drive electronics (multiplexer biases,

timing signals, and image I/O data) and an isolation box as shown in Fig. 1. There is also provision for image processing to precondition images before stimulating the retina—this is based on knowledge of retinal processing but is not covered in this paper.

Instrumentation and Ancillary Electronics

The drive electronics are composed of a PC and two customized I/O boards that control and monitor the device. Being a PC-based system makes the operation more user-friendly for clinical trials outside of NRL. Input images that are sent to the device may be either live images from a camcorder or a digitally stored image sequence. Standard video images from a camcorder may be sent to the device after being digitized by a CODEC on the PC card. Alternately, an image sequence, digitally stored on the PC, may be used as input to the device. The digital images and synchronous timing signals are sent to the device from the PC through an isolation box such that the system meets all Food and Drug Administration (FDA) electrical safety requirements.

Isolation Box

This is a critical safety device that is needed to eliminate any possibility of electrical shock. It contains an extreme isolation power supply and a printed circuit board. It electrically isolates the device from the outside world, provides dc biases and timing signals, and passes image input and output video. The timing signals and video are isolated using optocouplers. The isolation box can adjust the gain and offset of all signals with control potentiometers mounted on its front panel.

Laboratory Measurements

There are two primary operating modes that the multiplexer sequences through during each image frame: 1) "Write" image into unit cells (while charge equilibrating); and 2) Stimulate and "read" from the output multiplexer. Characterizing the device performance involves measuring the electrical current output into tissue (a saline bath acts as an equivalent medium) as a function of pixel value and biphasic pulse amplitude. The device is capable of producing currents of more than 1 μA per electrode with no electrode damage in preliminary saline testing. The level of electrical current that can be generated by each unit cell is shown in Fig. 6. The measured performance very closely matched design predictions. During laboratory testing, the device survived many hours of saline testing, indicating that the device should easily withstand one-hour clinical tests. The signal-to-noise ratio of individual pixels is estimated to be on the order of 100:1. Images recorded from the device output multiplexer were of good quality as shown in Fig. 1.

CLINICAL TRIALS AND COMMERCIALIZATION

Preclinical trials were performed by a surgical team at the MedStar Research Institute and Washington National Eye Center under separate DARPA funding to evaluate the NRL device, to develop surgical techniques (based on standard intraocular surgical methods and materials), and to study related issues pertaining to safety and biocompatibility.

The initial findings by the MedStar team were that acute surgical experiments with the NRL device, while challenging, are technically feasible for human experi-

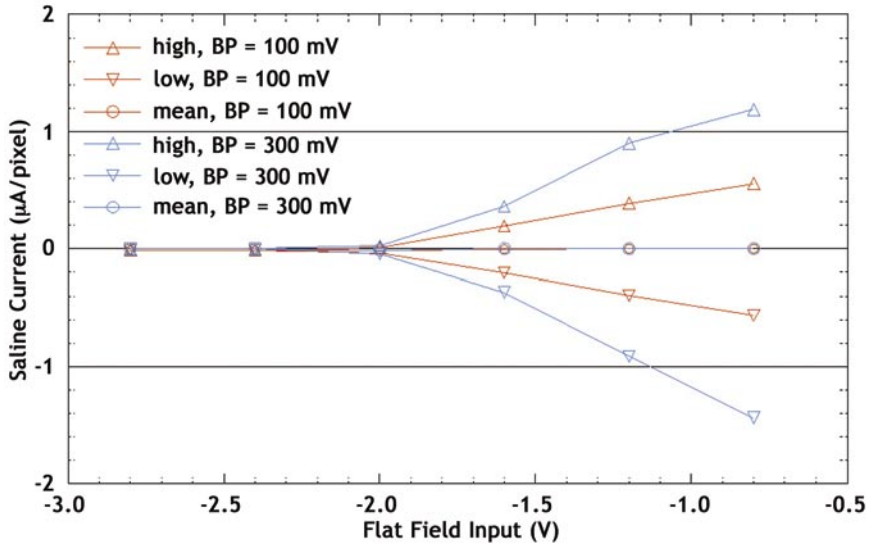

FIGURE 6
Plot of the level of electrical current that can be generated by each unit cell as a function of pixel value and biphasic pulse (BP) amplitude.

ments. More specifically, future human experiments should not result in any eye damage (even in the case of blind patients) while significantly advancing the state of knowledge of visual perception, neural-electronic interfaces, and related image preprocessing.

The NRL device is a unique system for demonstrating a high-resolution retinal prosthesis, but was conceived as a pathfinder for wireless implementations of the same technology. Regarding commercialization, negotiations for licensing agreements and cooperative partnerships are currently under discussion between the NRL Technology Transfer Office and biomedical companies.

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