Chapter 7
The Boston Retinal Implant

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Abstract The Boston Retinal Implant Project has developed a subretinal, hermetically-enclosed, chronically-implantable vision prosthesis to restore some useful vision to people with degenerative retinal diseases, especially retinitis pigmentosa and age-related macular degeneration. Our implant attaches to the outside of the eye, with only the electrode array entering the eye, carrying over 256 independently-configurable retinal stimulation channels. Our device receives wireless power and data from an inductive link, and inbound data includes image information in the form of stimulation commands containing current amplitudes and pulse widths. Outbound data includes status information on the implant and measurements of electrode voltages. A custom-designed integrated circuit chip is packaged in an 11 mm-diameter titanium case with a ceramic feedthrough, attached to the side of the eye. The chip decodes the stimulation data, creates biphasic, charged-balanced current pulses, and monitors the resulting voltages on the stimulating electrodes. The electrode array is a thin, flexible, microfabricated film carrying hundreds of wires to exposed electrodes in the eye. The electrodes are coated with sputtered iridium oxide film to allow much greater charge transfer per unit area by means of reversible faradaic reactions. The Boston Retinal Implant is being manufactured and tested in pre-clinical trials for safety, with plans to begin clinical trials soon.

Keywords Retinal prosthesis • Retinal implant • Neural stimulation • Subretinal • Medical device • Power and data telemetry • Hermetic packaging

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Key Points

- The Boston Retinal Implant delivers over 256 independently-configurable channels of stimulating current to create vision.
- Our device attaches to the outside of the eye, with the electrode array entering the eye, resting in the subretinal space.
- We have implemented several redundant safety features to prevent corrupted messages, overstimulation, and charge imbalance.
- Our device is being tested in preclinical studies, with plans to begin clinical trials soon.

Overview

The field of retinal prosthetics emerged in the late 1980s, and the Boston Retinal Implant Project was one of the first two research projects that were formed. The development of these implants was enabled by rapid advances in microelectronic technology [1, 2]. These devices require a large number of stimulating channels in a package small enough to conform to the eyeball. The convergence of technological improvements in integrated circuit (IC) chip fabrication, microelectromechanical systems (MEMS) fabrication, electrode materials fabrication, and hermetic packaging manufacturing has allowed implanted neural stimulators to become small enough and to have a large enough number of channels to create prostheses with a reasonable hope of restoring vision to the blind.

The overwhelming majority of patients over age 40 years in industrialized countries who are either "legally-blind" (<20/200 in their better seeing eye) or "visually-impaired" (20/40 or worse in their better seeing eye) have some form of neural blindness, usually either age-related macular degeneration (AMD), retinitis pigmentosa (RP), diabetic retinopathy, or glaucoma, and there are no satisfactory treatments to restore vision for any of these conditions. While the degenerative diseases AMD and RP cause loss of the photoreceptors in the retina, they spare the retinal ganglion cells. Electrical stimulation of these ganglion cells, or of the retinal network upstream from them, generates visual percepts that can form the basis of a visual prosthesis.

A visual prosthesis requires a number of different technological elements (Fig. 7.1). First, a method for collecting visual information is required. This is often a small electronic camera outside the body, usually mounted on a pair of glasses, but it is occasionally an implanted photodiode array. Second, the prosthesis requires a method for sending power to the implanted device, and, in the case of an external camera, for sending image data to the device. This is often accomplished with inductive coupling between wire coils, though a number of optical power transfer strategies have been explored. Circuitry is required to generate stimulating currents in a safe and controlled way, and small and charge-efficient electrodes are required that can safely deliver currents to the target tissue without creating dangerous

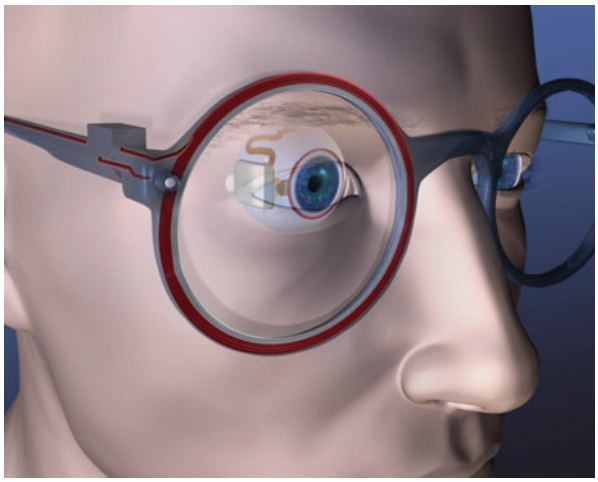

Fig. 7.1 The Boston retinal implant concept. The patient wears a camera mounted on a pair of glasses. Images are sent to a smart-phone-sized controller unit (not shown), which processes the images before sending the pertinent image data, along with power, wirelessly to the implanted device. The implant decodes the data and electrically stimulates the retinal tissue to create artificial vision

reduction and oxidation reactions. Because the implant must be quite small to attach to the eye, the circuitry is usually a custom-designed integrated circuit chip. The electrodes are often in the form of thin-film microfabricated arrays. The stimulating electrodes themselves are usually planar, but electrodes that penetrate into the retina have been explored by our group as well. Finally, a method is required for protecting the sensitive electronics from the body's saline environment. Classically, this is done using hermetic packaging, with a titanium case brazed to a ceramic block with platinum feedthroughs, but microfabricated methods are being explored.

The Boston Retinal Implant Project has chosen an approach using an external camera mounted on glasses. The image data go to a small external electronic unit that processes the image to select the most relevant few 100 pixels to send to the implant. The external unit also includes batteries and the wireless power and data transmitter. This approach provides substantial flexibility to modify image processing algorithms using external commands, or to implement multiple image processing modes, to best suit a specific patient and a specific visual situation.

The other significant design choice that we have made pertains to the specific location of the stimulating electrodes in the retina (Fig. 7.2). The electrodes may be placed on top of the inner retinal surface (epiretinal), beneath the retina (subretinal), or in a number of locations farther outward in the eye (e.g., the suprachoroidal space). We initially explored an epiretinal approach, but switched to a subretinal approach for a number of design reasons. First, the subretinal location enables an *ab externo* surgical approach, where the implant is attached to the outside of the eye, releasing its excess heat to less thermally sensitive tissues than the retina. It is possible to use an *ab externo* approach to the epiretinal surface, but it requires a relatively long electrode cable that enters the eye very near the limbus, near where the conjunctiva attaches to the eye. At this location, a device is prone to erosion through the delicate conjunctiva, and chronic hypotony of the eye has also been a complication of this approach. And, once in the eye, the electrode cable must extend to the back surface of the eye, which imposes

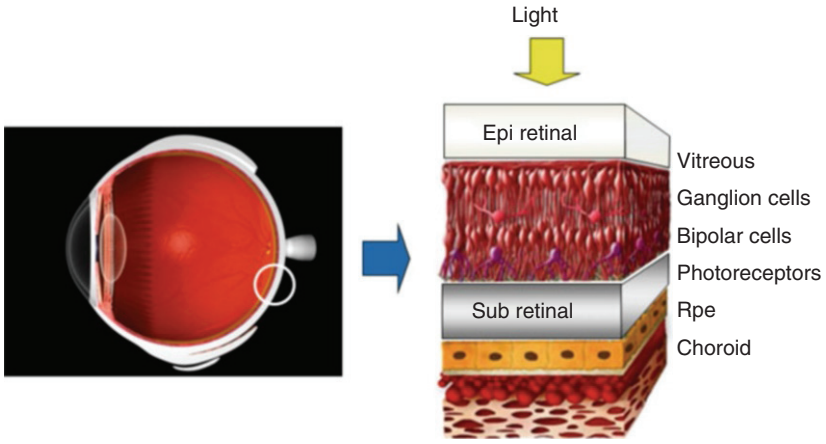

Fig. 7.2 Retinal electrode locations. Stimulating electrodes are often placed on the inner surface of the retina (epiretinal) or under the retina, between the neural cells and the retinal pigment epithelium (RPE), (subretinal). Some arrays are placed farther from the tissue, either underneath the choroid (suprachoroidal), or outside the sclera (trans-scleral)

undesirable mechanical factors that can challenge conformal alignment of the electrode array across the retina. In this regard, an epiretinal electrode requires some method of attachment to the retina, usually a tack through the retina, whereas, an array in the subretinal space is held in place without the need for external fixation. This overview of relative advantages and disadvantages of the various approaches is not intended to suggest that one approach is definitively better than the other. Ultimately, preferred methods will have to be validated with long-term human implants, and our group has yet to perform such tests.

Background

While the concept of electrically stimulating retinal ganglion cells of a patient with outer retinal degeneration seemed like a plausible therapeutic strategy, proof-of-concept experiments were a prudent step before launching into the arduous process of designing a chronic implant. In the case of BRIP, initial animal trials were performed by delivering electrical stimulation to the retina through a long connecting cable containing an electrode array, which was placed in contact with the epiretinal surface. The cable was connected to external electronics that provided stimulating current, and recording electrodes were placed into the skull over the visual cortex. This approach revealed cortical responses that were linked to photic stimuli and to electrical stimuli in separate trials, with delays consistent with synaptic transmission from the retinal ganglion cells to the visual cortex. These experiments showed that electrical stimulation of the retina can send neural signals to the cortex, but this type of experiment revealed nothing about the quality of the visual percepts.

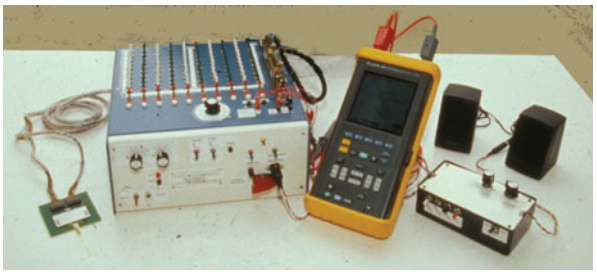

Fig. 7.3 The portable, battery powered stimulation system used in our acute human trials. The blue and white box is the 100-channel stimulator, connected via a 7-ft cable to a green circuit board containing the electrode array (at *left*). A portable battery-powered oscilloscope monitors the voltages, and a set of speakers creates a tone to alert the subjects to the timing of the stimulus

To learn something about the human perceptual response to electrical stimulation of the retina, our group performed six acute human retinal stimulation trials between 1998 and 2000 [3, 4]. In these experiments, we used the same approach developed in animal tests to deliver electrical stimulation to the retina. Subjects were chosen who had outer retinal degeneration that had progressed to a severe state, with no better than hand motion perception in the worse eye, which was always the eye studied. One subject had normal vision, but had orbital cancer, which required removal of the eye; this patient allowed us to deliver electrical stimulation to the retina just prior to enucleation. Our electrode array was a 10-μm-thick polyimide film containing between 20 and 100 planar electrodes. The use of an ultra-thin substrate like this was novel for the field of visual prosthetics. The electrodes in the first experiment were 50 μm in diameter, and in later experiments, electrodes 100 and 400 μm in diameter were added. The electrode was coated with an iridium oxide film, which is capable of safely delivering more than ten times the charge of a platinum electrode of the same size. The back end of the electrodes, outside the eye, was connected via a cable to the stimulator system (Fig. 7.3). The battery powered stimulator delivered current to up to 100 electrodes from ten current sources, allowing concurrent and/or sequential stimulation.

These human trials gave a number of important results. First, and most importantly, they showed that electrical stimulation of the retina produces distinct, perceivable visual events. These visual percepts could be combined to form recognizable lines, but more complicated structures were difficult to achieve with a severely visually impaired subject, lying on an operating room table, receiving visual percepts in their periphery for a few hours. We also learned that the thresholds for electrical stimulation of retina were reasonable, and were within the safe charge density range for iridium oxide, but that the thresholds were sensitive to the electrode position.

While the results of these human trials were encouraging, they showed the need for a chronic retinal implant, one that would allow subjects to learn to use the new visual information over time. Since then, our group has developed five generations of implantable devices, each with progressive improvements in power and data telemetry, stimulation safety, number of stimulating channels, digital controls, and

hermetic packaging [5–8]. Our designs also evolved to improve surgical access for electrode array insertion and to reduce irritation of sensitive parts of the eye, especially the conjunctiva. The rest of this chapter will describe the technical details of the latest design of the Boston Retinal Implant.

Device Requirements

The Overview section above describes the technical elements of a retinal prosthesis. Here we expand upon that information to now include specific requirements for our device. The first element, the camera, is not heavily constrained in this design, except in size. With an implant driving a few hundred electrodes, the number of pixels in any camera will be too large by several orders of magnitude. However, the camera needs to be integrated into the glasses worn by the patient, so it should be small and lightweight. The wireless power and data system should be robust, first and foremost. It should be tolerant of quick movements of the eye, as well as slower shifts in the position of the glasses, and it should be able to adjust the power delivered to compensate for movements of the coil as well as changes in the power required by the chip. The telemetry system should be moderately efficient to conserve battery power, but robustness should not be sacrificed for efficiency. Finally, the telemetry system should be able to transmit at a sufficient data rate to supply stimulation information to all electrodes at the target simulation rate with appropriate systems in place to check data accuracy, and the system should be able to transmit information out from the implant, though at a slower rate.

The implanted component should include circuits with the ability to deliver precise stimulating currents, with sufficient flexibility to explore a range of stimulation parameters to create optimal visual percepts. The circuits should be small in size to fit in a package that can be attached to the eye, and should utilize low-power design to save battery life and to avoid heating the eye. In addition, the stimulating circuit should include redundant safety features to prevent dangerous electrochemical reactions and damage to the retinal tissue, and to detect and report any faults that develop over time.

The electrode array should be thin and flexible, but tough and robust enough to stand up to handling during surgery and normal movements of the eye. The stimulating electrodes should be made of a material that can convey sufficient charge to the retina to stimulate tissue with a broad dynamic range without causing irreversible reduction or oxidation reactions. The array construction should enable hundreds of connections and be small enough to pass through a relatively small incision in the eye. The materials used in the array in the electrode sites should be biocompatible, not inducing inflammation in the retinal tissue.

The implanted package should be hermetic, preventing the ingress of water over the lifetime of the device, in our case, for over a decade. This is particularly challenging due to the very small internal volume of the device. In addition, the package must be small, thinner than 2 mm in height and with a diameter on the order of 1 cm, with hundreds of feedthroughs.

The combination of these requirements is a serious engineering challenge requiring custom wireless circuit design, custom chip design, the development of new fabrication processes for electrodes, and the development of new medical device packaging technologies.

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The first element in the logical stream of events, the camera and glasses, has been the last component that we have chosen to build. Small cameras are improving every year, and an off-the-shelf camera should be easily integrated into custom glasses. Therefore, our group has delayed the design and manufacturing of the camera and glasses until the more complicated implanted device is fully completed and in preclinical testing.

Wireless Power and Data

The inductive telemetry system consists of a primary coil mounted on the glasses, a secondary coil attached to the anterior surface of the eye (just posterior to the limbus and beneath the conjunctiva), and associated transceiver circuits. Approximately 30 mW is transmitted to the implant, with feedback to control the received power.

Custom Integrated Circuit Design

The retinal implant requires several unique features that demand a custom-designed integrated circuit chip. Specifically, very large numbers of current sources, as well as the associated safety features, are not available in off-the-shelf chips. Some of the digital control features could be implemented with commercially available systems, but with a cost of size that is unacceptable for an implant that needs to be small enough for this ocular application. As such, our group designed and tested a custom integrated circuit chip for our prosthesis.

The forward wireless power and FSK data link from the external controller to the implant chip that our group has built (Fig. 7.4) transmits and receives data with very high signal-to-noise ratio (SNR) and zero errors over thousands of packets to the receiver.

The more than 256 independent current sources deliver charge-balanced currents, ranging from 0 to 126 μA, in steps of 1 μA. Individual stimulation phase widths range from 17.7 to 4500 μs, in steps of 17.7 μs. Voltage supplies for the current sources can be set to ±4 V for normal operation, or up to ±8 V for higher current source compliance if needed. Stimulus commands for small numbers of

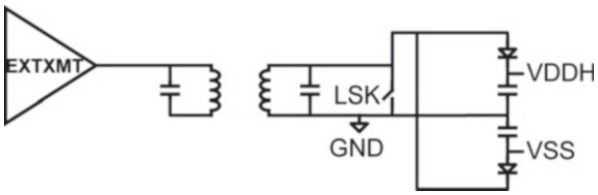

Fig. 7.4 Power and data transmission system. The transceiver block diagram shows the external transmitter and coil, secondary coil, secondary dual half-wave rectifier to establish Vddh and Vss, and LSK switch

electrodes can be sent at a stimulation refresh rate exceeding 400 Hz, or commands can cycle through groups of electrodes to drive every electrode with a refresh rate exceeding 60 Hz.

Safety features include stimulus charge limits, error checking on data transmission, comprehensive self-test and performance monitoring, and configuration pins to change operating modes or to lock out settings that might somehow cause harm. Each message from the external controller to the IC can result in a set of stimulus pulses on a subset of the electrodes, and each message generates a corresponding response from the implant IC with chip and electrode status, and any other requested data. Radio communication errors are nearly eliminated by the use of 32-bit cyclic redundancy checks (CRCs). A single data packet includes every stimulation parameter for every electrode to be stimulated in the subsequent time frame. No individual message can cause harm, and messages with a bad CRC merely result in missed stimulus pulses, drastically reducing the chances of delivering an unintended stimulation that may be dangerously imbalanced or larger than the safe limits. Several features also work to ensure operation with safe levels of electrode polarization. While allowing both high-current short-duration pulses and low-current long-duration pulses, the IC has hardware-enforced charge limits, guided by our prior electrode characterization work [5]. Configuration pins allow the limits to be changed for compatibility with a range of electrode sizes.

One particular concern is the polarization of the electrode-tissue interface. If that interface is driven outside the electrochemical water window of −0.6 to +0.8 V, charge injection occurs in the form of oxidation or reduction of water, which can be biologically damaging and mechanically damaging to the electrodes [9]. Our prosthesis uses sputtered iridium oxide film (SIROF) electrode sites, which have the benefit of allowing very high charge densities (exceeding 1 mC/cm^2) with reversible electrochemical reactions, but which have the possibility of suffering mechanical failure if the interface is repeatedly driven outside the water window. However, due to the non-linearity and distributed nature of the electrode impedance, it is very difficult to measure the electrode-tissue interface while the stimulus current is being driven [10]. Therefore, we measure the electrode polarization in the middle of the biphasic current pulse, during the interphase interval (Wip in Fig. 7.5).

During the time between biphasic pulses, each electrode is grounded (shorted to the case, which serves as a counter electrode) for at least 200 μs before any stimulus,

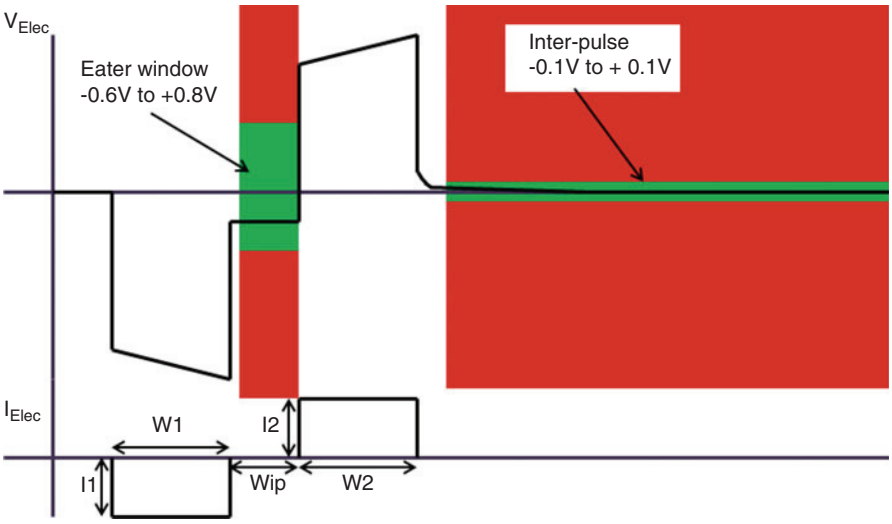

Fig. 7.5 Target ranges for safety monitoring. During the inter-phase interval, a monitor circuit ensures that the electrode-tissue interface voltage remains within the water window, the range of voltages at which water is not oxidized or reduced to release gas bubbles. During the period between biphasic pulses, a monitor circuit ensures that the electrode voltage remains very close to the counter electrode (GND) after it is shorted with a MOSFET switch

and its voltage is monitored to ensure that the electrode is fully depolarized, and monitored again between phases of the biphasic current pulse to ensure that electrode polarization is within safe limits (see Fig. 7.5) [11]. The VDDH and VSS power supplies prevent excessively large voltages from being driven on electrodes. In addition, the integrated ADCs periodically sample the voltage waveforms on each electrode, sending back detailed measurements to the external controller; this method allows open and short circuits of damaged electrodes to be detected, as well as changes in electrode-tissue impedance and responses over time.

Any subset of electrodes can be driven in a given stimulus cycle, and electrodes can be configured as sources of current or as local current sinks (returns) to provide current steering capabilities. Power consumption is minimized in a number of ways, which ultimately limits the RF energy the recipient must be exposed to while the implant is active.

Microfabricated Thin-Film Multi-electrode Array

The intimate interface between the implanted electronics and the retinal tissue is the stimulating electrode. Care must be taken in the design, material choice, and fabrication of these electrodes, to prevent mechanical damage, toxic material release, or unwanted electrochemical reactions. Our electrode arrays are microfabricated to be thin and flexible, and use biocompatible and biostable materials. The stimulation

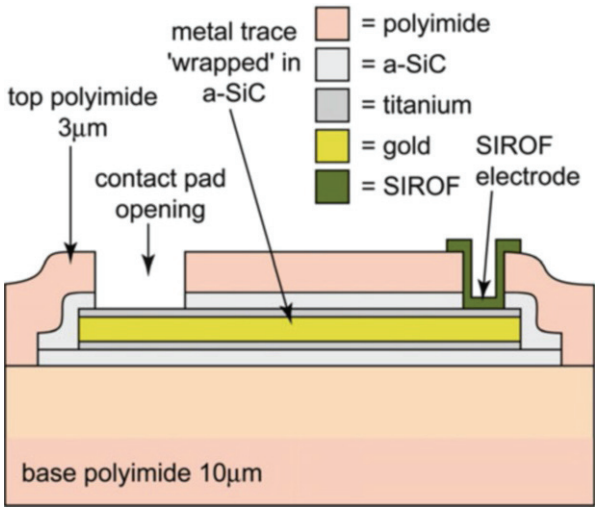

Fig. 7.6 Electrode array fabrication. Schematic cross-section diagram showing the electrode array fabrication process

sites use sputtered iridium oxide film (SIROF) to provide the capability of delivering up to 1 mC/cm^2 of stimulus charge using reversible faradaic reactions.

The electrode arrays, shown in (Fig. 7.6), were manufactured in a microfabrication facility using thin-film methods [5]. Using a silicon wafer as a foundation, layers of polyimide, titanium, and gold are created and patterned to create the wiring and openings for the electrodes. Long-term soak tests revealed that the polyimide interface can delaminate with water absorption, so layers of silicon carbide were placed above and below the metallization layers. This SiC sandwich prevented delamination during pulsing soak tests exceeding 1 year. The electrode sites were then coated with sputtered iridium oxide film (SIROF) [12–14]. The final thickness of the electrode arrays is 15 µm.

Hermetic Retinal Implant Packaging

The first retinal implant that our group implanted in an animal in 2008 was coated with poly(dimethylsiloxane) [5], allowing that device to survive up to 10 months before being explanted. However, longer-term implantation requires a barrier that is impervious to water vapor [15]. This requires the crystalline structure of a metal or ceramic. To protect the implanted circuits in the body, we have developed a small hermetic enclosure made of titanium and alumina ceramic, with more than 256 individual electrical feedthroughs [16]. The ceramic feedthrough comprises several layers of green ceramic, with punched holes filled with biocompatible conductive material. The feedthrough layers are stacked and co-fired, machined to ensure final size, and then brazed to the titanium case. The case is circular, and is roughly 11 mm in diameter, small enough to attach to the outside of the human eye in the socket.

Fig. 7.7 Hermetic case assembly. From *left* to *right*: An exploded view of the case, showing titanium case pieces, feedthrough, and polyurethane header. A view of the feedthrough on a US nickel 5-cent coin. Circuit board and chip soldered into the case. Electrode array bonded to the outside of the feedthrough

A small, circular circuit board holds the chip and the small number of required resistors, capacitors, and diodes. The board is 10.6 mm in diameter and includes six metal layers with traces as small as 30 μm wide. The board contains connections between the chip and other components, as well as vias connecting the chip pads on the top layer to feedthrough pads on the bottom layer. The bare die ASIC is flip-chip assembled onto the top of the circuit board by reflowing solder bumps on the chip pads, and the off-chip components are soldered onto the board. The bottom surface of the board is attached to the inside surface of the feedthrough by reflowing solder bumps on the feedthrough pads. The titanium case is laser welded shut in a helium environment to enable hermeticity testing, and the electrode array is attached to the outside of the case by thermosonic bonding between gold surfaces electroplated onto both the array and the outside of the feedthrough. Finally, a molded polyurethane header is added over the array connections and is underfilled with epoxy. The feedthrough and hermetic package are shown in (Fig. 7.7). We expect this device to function in the body for at least the 5 years recommended by the FDA, with a target of 10 years. The device is meant to be explantable at the end of its life or in case of complications.

The co-fired ceramic feedthroughs of the package were tested for helium leakage, and measured for hermeticity. A helium leak rate of between 10^{-9} and 10^{-8} standard cc/s was measured across the devices. The moisture leak rate is typically about half that of helium, and with the internal volume of our implant, we expect a life of 5–10 years, though more careful helium leak tests need to be performed.

Current Status and Future Directions

The Boston Retinal Implant Project is currently manufacturing its chronic implant with over 256 channels. We are beginning pre-clinical animal studies required by the FDA, and we expect to enter a phase I pilot clinical trial of chronically-implanted devices in the near future.

We are also exploring a number of research directions for future implants. Our group has developed novel innovations in using varying voltages to take advantage

of knowledge of the electrode impedance to reduce stimulation power [17]. We are developing circuits that can improve the safety of retinal stimulation by eliminating the residual voltage that is inherent in charge-balanced biphasic current stimulation [18]. We are exploring novel electrode shapes that may deliver stimulus current closer to the target cells, and we are beginning to examine advanced packaging techniques that will allow us to scale the number of channels up toward 1000.

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