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Editors

Implantable Neural Prostheses 1

Devices and Applications

🐎 Springer

Editors

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Preface

Significant progress has been made in the development of neural prostheses to restore human functions and improve the quality of human life. Biomedical engineers and neuroscientists around the world are working to improve design and performance of existing devices and to develop novel devices for artificial vision, artificial limbs, and brain–machine interfaces.

This book, *Implantable Neural Prostheses 1: Devices and Applications*, is part one of a two-book series and describes state-of-the-art advances in techniques associated with implantable neural prosthetic devices and their applications. Devices covered include sensory prosthetic devices, such as visual implants, cochlear implants, auditory midbrain implants, and spinal cord stimulators. Motor prosthetic devices, such as deep brain stimulators, Bion microstimulators, the brain control and sensing interface, and cardiac electro-stimulation devices are also included. Progress in magnetic stimulation that may offer a non-invasive approach to prosthetic devices is introduced. Regulatory approval of implantable medical devices in the United States and Europe is also discussed.

Advances in biomedical engineering, micro-fabrication technology, and neuroscience have led to many improved medical device designs and novel functions. However, many challenges remain. This book focuses on the device designs and technical challenges of medical implants from an engineering perspective. We are grateful to leading researchers from academic institutes as well as design engineers and professionals from the medical device industry who have contributed to the book. Part two of this series will cover techniques, engineering approaches, and R&D advances in developing implantable neural prosthetic devices. We hope a better understanding of design issues and challenges may encourage innovation and interdisciplinary efforts to push forward the frontiers of R&D of implantable neural prostheses.

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List of Acronyms

A1	Primary auditory cortex
ABI	Auditory brainstem implant
ACI	Auditory cortex implant
AF	Activating function
AF	Atrial fibrillation
AIROF	Activated iridium oxide film
AMD	Age-related macular degeneration
AMI	Auditory midbrain implant
ANI	Auditory nerve implant
ASIC	Application specific integrated circuit
AV	Atrioventricular
BBS	Bicarbonate buffered saline
BCI	Brain–machine interface
BJT	Bipolar junction transistor
BON	Bed of nails
CCD	Charge coupled device
CFR	Code of federal regulations
CHF	Congestive heart failure
CI	Cochlear implant
CIS	Continuous-interleaved-sampling
CL	Current level
CMOS	Complementary metal-oxide semiconductor
CRT	Cardiac resynchronization therapy
CS	Coronary sinus
CSF	Cerebrospinal fluid
CSP	Chip-size packages
cTMS	Controllable pulse-width TMS
CV	Cyclic voltammetry
DAC	Digital analog converter
DBS	Deep brain stimulation
DRIE	Deep reactive ion etching
DRth	Excitable dorsal root
DSP	Digital signal processor

EEP	Electrically evoked potential
EIROF	Electroplated iridium oxide film
EIS	Electrochemical impedance spectroscopy
EMI	Electromagnetic interference
ERG	Electroretinograms
ESC	Environmental stress cracking
EtO	Ethylene oxide
FBC	Field balancing and cycling
FDA	Food and Drug Administration
FEM	Finite element method
FES	Functional electrical stimulation
FMEA	Failure modes & effects analysis
FMS	Functional magnetic stimulation
FOA	Focus of attention
FRCB	Frequency-related conduction block
FS	Field steering
GABA	Gamma-aminobutyric acid
GCL	Ganglion cell layer
GERD	Gastroesophageal reflux disease
GPi	Globus pallidus internus
HDE	Humanitarian device exemption
HMD	Head-mounted display
HUD	Humanitarian use device
IC	Inferior colliculus
ICC	Its central nucleus
ICD	Implantable cardioverter defibrillators
ICP	Inductively-coupled plasma
IDE	Investigational device exemption
IGBT	Insulated gate bipolar transistor
ILM	Internal limiting membrane
INL	Inner nuclear layer
IPG	Implantable pulse generator
IPL	Inner plexiform layer
IR	Infrared
IRB	Institutional review board
IR drop	Voltage drop across a resistance - current (I) x resistance (R)
IrOx	Iridium oxide
LCR	Inductance capacitance resistance
LES	Lower esophageal sphincter
LGN	Lateral geniculate nucleus
LiI	Lithium iodide
LPCVD	Low-pressure chemical vapor deposition
MEA	Microelectrode arrays
MEMS	Micro-electro-mechanical system

MIDAS	Migraine disability assessment
MIO	Metal ion oxidation
MPTP	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
NF2	Neurofibromatosis type 2
NFL	Nerve fiber layer
NRT	Neural response telemetry
OCT	Optical coherence tomography
OLM	Outer limiting membrane
ONL	Outer nuclear layer
OPL	Outer plexiform layer
PCU	Prosthetic control unit
PBS	Phosphate-buffered saline
PD	Parkinson's disease
PDCA	Plan-do-check-act
PDMS	Polydimethylsiloxane
PECVD	Plasma-enhanced chemical vapor deposition
PGC	Programmable gain control
PMA	Premarket approval
PSA	Pacing system analyzer
PSD	Power spectral density
PU	Pressure ulcer
PW	Pulse width
RF	Radio frequency
RMS	Root mean square
RP	Retinitis pigmentosa
RPE	Retinal pigment epithelium
rTMS	Repetitive TMS
SBON	Slanted bed of nails electrode
SC	Superior colliculus
SCR	Silicon controller rectifier
SCS	Spinal cord stimulation
SD	Standard deviation
SDRAM	Synchronous dynamic random access memory
Si_3N_4	Silicon nitride
SiC	Silicon carbide
SiO_2	Silicon dioxide
SNR	Signal-to-noise ratio
SIROF	Sputtered iridium oxide film
SOI	Silicon-on-insulator
STN	Subthalamic nucleus
SVO	Silver vanadium oxide
Ta_2O_5	Tantalum pentoxide
T cell	Transmission cell
TDMA	Time domain multiplexed access

TiN	Titanium nitride
TMS	Transcranial magnetic stimulation
TTS	Transverse tripolar system
V1	Visual cortex
VEP	Visual evoked potentials
UF	Urgency frequency syndrome
UNCD	Ultrananocrystalline diamond
UUI	Urinary urge incontinence
VF	Ventricular fibrillation
VLSI	Very large-scale integrated circuit

Microelectronic Visual Prostheses

David D. Zhou and Robert J. Greenberg

Abstract Research efforts worldwide are developing microelectronic visual prostheses aimed at restoring vision for the blind. Various visual prostheses using neural stimulation techniques targeting different locations along the visual pathway are being pursued. Retinal prostheses have proved to be capable of offering blind subjects in advanced stages of outer retinal diseases the opportunity to regain some visual function. With relatively low-density retinal implants, simple visual tasks that are impossible with the blind subject's natural light perception vision can be accomplished. Blind subjects can spatially resolve individual electrodes within the array of the implanted retinal prosthesis and can use the system to discriminate and identify oriented patterns. This chapter reviews progress in the development of visual prostheses including visual cortex and optic nerve stimulation devices and retina stimulation devices such as epiretinal, subretinal, and extraocular implants. Second Sight Argus 16 and Argus II 60-electrode Retinal Implants are described. Some engineering challenges for the development of visual prostheses, especially retinal prostheses, are discussed.

1 Introduction

Blindness has a devastating impact on people's quality of life and economy. In 1997 the US Census Bureau reported that about 8 million individuals over the age of 15 had difficulty seeing and of those, 1.8 million were unable to read [1]. Hereditary retinal degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), are among the more frequent causes of blindness through photoreceptor loss. In the United States, retinal blindness alone costs $4 billion annually in lost benefits and taxable income to the government. RP has an incidence rate of approximately 1 in 4000 births, and

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therefore affects more than 100,000 people in the United States [2]. It is projected that the incidence for AMD among people aged over 65 may be as high as 5.5% in 10 years [3, 4].

Inspired by the success of cochlear implants, which restore hearing for the deaf, research efforts worldwide are developing microelectronic visual prostheses (visual implants) aimed at restoring vision for the blind [5–10]. Many recent developments from research teams to industrial groups working on visual prostheses have raised hopes for the possibility of creating retinal implants and other strategies for restoring vision in blind subjects. In particular, a retinal prosthesis has the potential to provide increased vision to some subjects who are blind from degeneration of the outer retina. In fact, there is theoretical and some experimental clinical evidence that suggests that direct electrical stimulation of the retina might be able to provide some vision to subjects who have lost the photoreceptive elements of their retinas.

This chapter will review the progress of the development of visual prostheses, especially in retinal implants. Some technical challenges will be discussed.

2 Biomedical Engineering Approaches for Restoring Vision to the Blind

2.1 Visual Pathway

The visual pathway consists mainly of the eye, optic nerve, lateral geniculate nucleus (LGN), and visual cortex (also known as striate cortex or V1) (Fig. 1). When the light reaches the retina through the cornea and the pupil, photoreceptors on the outer boundary layer of the retina membrane convert photons into electrical neural signals. These signals are processed by cells in the retina structure and are sent to the brain along the optic nerves. Optic nerves send
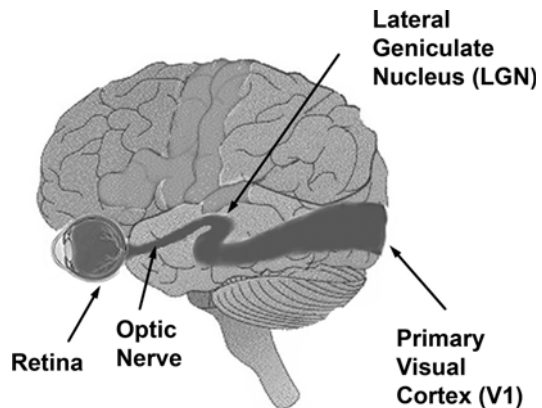

Fig. 1 Visual pathway

neural signals to the visual cortex of the brain via the LGN, a relay station deep in the brain hemisphere. Blindness can result from diseases or injuries to any part of this visual pathway. For example, glaucoma may cause damage to the optic nerve due to excessively high intraocular pressure, while stroke, brain tumor, and head trauma may cause damage to the visual cortex.

2.2 Eye and the Retina

The eyeball is slightly ellipsoidal and has a volume of about 10 cm^3 in an adult 18–30 years of age [11]. The axial length is approximately 24 mm from the cornea to the retina. The space inside the eye has a volume of about 4–6.5 ml and is filled with clear vitreous humor. The vitreous is a gel that consists of collagen fibers that are separated and stabilized by hyaluronic acid [12]. Approximately 98% of this gel is water; diffusion of low molecular-weight solutes such as inorganic ions, glucose, and amino acids is unimpeded through the vitreous.

Table 1 lists the concentrations of some chemicals in the vitreous humor [13]. Oxygen is largely supplied by the atmosphere. The major substrate for respiration in the retina is glucose. Most of the glucose ($\sim$70%) utilized by the retina is converted to lactate. Glutamate, one of many neuro-active amino acids, has been found in higher concentration within the retina. The glutamate is actively metabolized by normal retina tissue. Vitrectomy and subsequent vitreous fluid exchange alter chemical and physical properties of the vitreous. A study by Manzanas et al. [14] indicated that changes in proteins, lactic acids, and ascorbic acids return to normal after 7 days.

Table 1 The concentrations of some chemicals in the vitreous humor [13] in comparison to those in plasma

Chemicals	In plasma	In vitreous
Na^+	146 μM	144 μM
Cl^-	109 μM	114 μM
K^+	–	7.7 μM
HCO_3^-	28 μM	20–30 μM
Ascorbate	0.04 mM	2.21 mM
Lactate	10.3 mM	7.78 mM
Glucose	6 mM	3.44 mM
Hyaluronate	–	32–240 μg/ml
Collagen	–	286 μg/ml
L-Glutamate	–	$\sim$0.1–10 μM

The human retina that lines the back of the eye is approximately 250 μm thick and resembles a thin single ply wet tissue paper in strength. The thinnest part of the retina, about 150 μm, is at the center of the fovea, while the thickest part of the retina at the fovea rim is about 400 μm. The human retina is a delicate multilayered organization of neurons, cells, and nourishing blood vessels (Fig. 3) [15]. The retina is organized both vertically and horizontally.

Fig. 2 The human eye
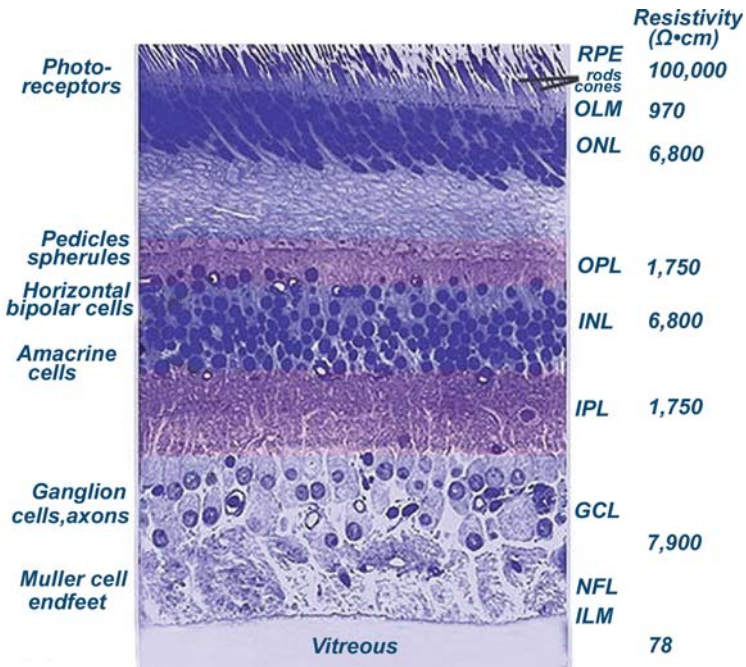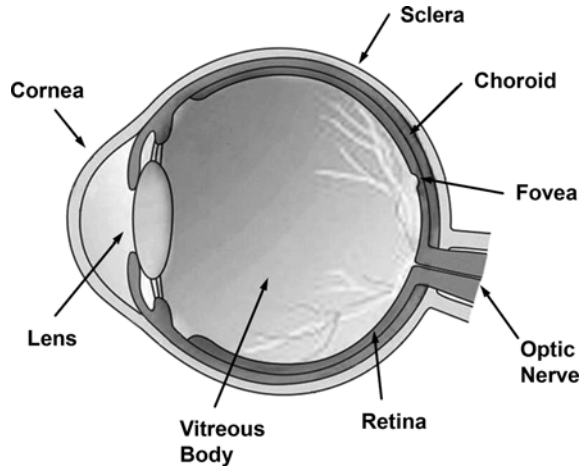
Fig. 3 The human retina layered structure and retinal neural cells. From *top* to *bottom*, the retina layers are: RPE, the retinal pigment epithelium, rod and cone layer; OLM, outer limiting membrane; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, nerve fiber layer; and ILM, internal limiting membrane (image adapted from Ref. [15] with permission). Listed on the right side are the resistivities of different retinal layers [17]

The vertically oriented cells are photoreceptors of rods and cones, the bipolar cells and the ganglion cells. The horizontally oriented cells are the horizontal cells and the amacrine cells.

A circular field of approximately 5–6 mm around the fovea is considered the central retina, and it is thicker than the peripheral retina due to increased packing density of photoreceptors. This central retina area is a preferred site for a retinal implant.

Vitreous has resistivity similar to saline (60–80 $\Omega \cdot cm$). However, the layered retina has much higher impedance than vitreous [16]. Estimated conductivity data from multiple sources and unpublished data are listed in Fig. 3 [16, 17]. Each layer in the retina has different resistivity. In particular, the retina pigment epithelium, the nuclear layers and the ganglion cell layer have been found to have higher resistivity than other parts of the retina.

2.3 Candidate Retina Diseases for the Retinal Implants

Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are two likely candidate diseases from retinal blindness that a retinal implant may help. For RP, the progression of the disease is generally slow, but the eventual impact on vision and quality of life is often devastating. For example, patients afflicted with RP for 25 years are usually left with a visual field of $10°$ or less (i.e., legally blind). As the disease progresses and further photoreceptor loss occurs, even this constricted field may be lost. Unfortunately, many of the people who have RP tragically lose their vision before the age of 40. Figure 4 shows a fundus photo of human retina with retinitis pigmentosa. The gradual onset and the relatively late age at which most RP and AMD patients become legally blind adds to personal and familial difficulties in adjusting to being blind [18, 19]. As lifespan increases within the United States and other counties, these degenerative diseases will affect a growing number of patients.
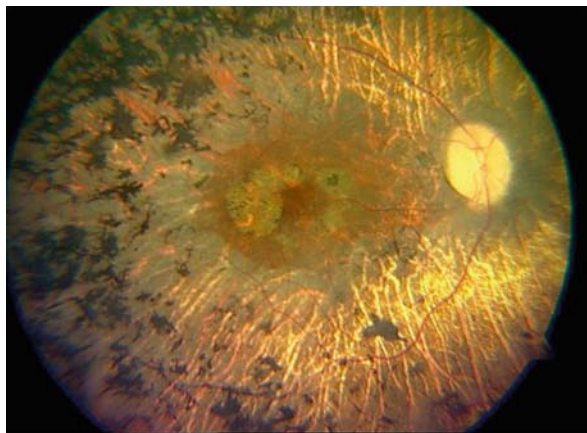

Fig. 4 Fundus photo of a human retina with retinitis pigmentosa

Macular degeneration results in legal blindness. In practical terms, this means vision of less than 20/200 or visual loss which results in the inability to watch TV, recognize faces, drive, or read. AMD is expected to become the single leading cause of legal blindness. Although some treatments to slow the progression of AMD are available, no treatment exists that can replace the function of lost photoreceptors [20].

2.4 Biomedical Engineering Approaches for Visual Implants

The possibility to restore vision in blind subjects using electricity began with the discovery that an electric charge delivered to a blind eye produces a sensation of light. This discovery was made by LeRoy in 1755 [21]. LeRoy passed the discharge of a Leyden jar through the orbit of a man who was blind from cataract and the subject saw "flames passing rapidly downwards". However, it was not until 1966 that the first human experiments in this field began with Brindley and Lewin's experiments on electrical stimulation of visual cortex [22]. While cortical stimulation approaches have made progress, it has been hampered by the complexity of the physiology [5]. The processing that has occurred by the time the neural signals have reached the cortex is greater than the more distal sites such as the retina. This results in more complex phosphenes being perceived by the blind subjects. Cortical prostheses provide additional risks such as intracranial hemorrhage and infection to a blind subject who has an otherwise normal brain. These factors and the lack of availability of implantable electronics have limited the clinical application of these devices.

The limitations of the cortical approach encouraged several groups worldwide over the past 20 years to explore the possibility of producing vision in patients with an intact optic nerve and damaged photoreceptors by stimulating the retina, the optic nerve, and recently the LGN [23–25]. Worldwide efforts to develop various microelectronic visual implants and to investigate various aspects of visual stimulations are increasing in recent years. Figure 5 shows some research teams and industrial groups in the United States, Europe, Asia, and Australia pursuing different approaches to restore vision in the blind.

3 Microelectronic Visual Implant Technologies

Depending on the location of stimulating electrodes, visual prostheses can be divided into three groups: retinal, optic nerve, and visual cortex (V1) including LGN devices. In retinal devices, three approaches are pursued and there are intraocular devices for epiretinal and subretinal stimulations and extraocular devices for transretinal stimulation. Retina stimulation differs from optic nerve
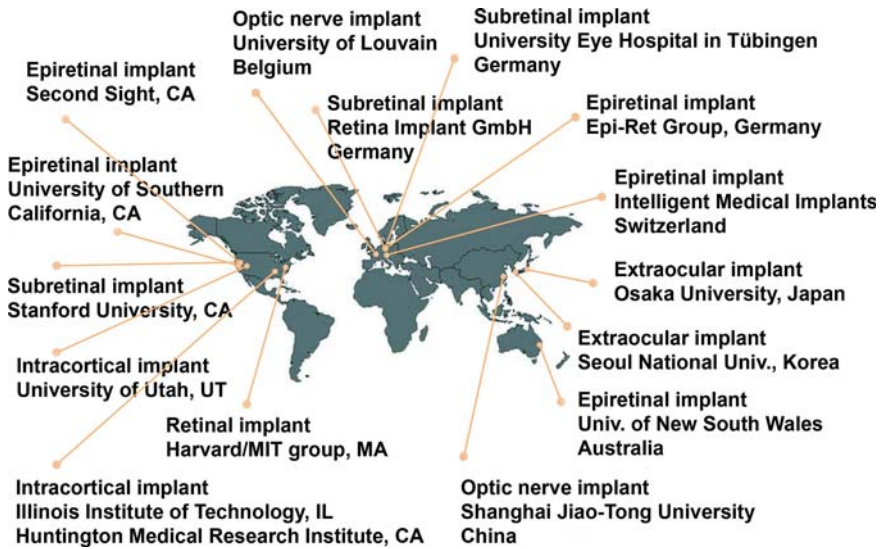
Fig. 5 Some research teams and industrial groups worldwide that are developing implantable visual prostheses

or cortex stimulation. Retinal implants stimulate remaining retinal neural cells to bypass lost photoreceptors and allow the visual signal to reach the brain via the normal visual pathway.

3.1 Retinal Stimulation and Retinal Implants

In retinal diseases like retinitis pigmentosa, blindness is caused by a loss of photoreceptors. Inspite of nearly complete degeneration of the retinal architecture, there is relative preservation of the inner retinal neurons [26, 27]. The approach of retinal stimulation by a retinal prosthesis positioned intraocular or extraocular is to electrically stimulate the remaining retinal cells. Three major approaches to retinal stimulation have emerged: epiretinal, subretinal, and extraocular (Fig. 6). Epiretinal approaches involve placing electrodes on the top side of the retina near ganglion cells [26, 28, 29], whereas subretinal approaches involve placing electrodes and most of the electronics under the retina in the location of the degenerated photoreceptors between the retina and the retinal pigment epithelium [30, 31]. In the extraocular approach electrodes are placed on the posterior scleral surface of the eye. Both epiretinal and subretinal implants have been tested chronically in humans while the extraocular devices have been limited to animal models and acute studies.
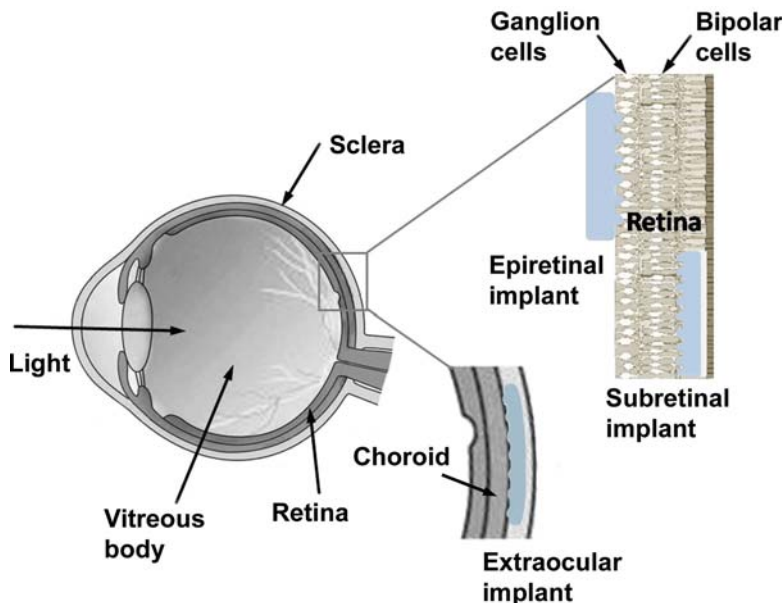
Fig. 6 Schematic of three approaches for an implantable retina implant: an epiretinal implant is placed on the ganglion cell side of the retina. A subretinal implant is positioned between the retina and the retinal pigment epithelium. An extraocular implant is placed on the scleral surface of the eye

3.2 Epiretinal Implant

The epiretinal approach has been pursued by several research teams [23, 28, 29, 32] and industrial groups [5, 35, 37]. Early acute experiments demonstrated that electrical stimulation could restore visual perception of dots and possibly more complex shapes. In one acute human trial by Humayun and co-workers [26], a single electrode array was placed onto the retina surface, no devices were implanted (Fig. 7). Prior to the introduction of the array, a majority of the vitreous gel was removed. A stimulus was transmitted to the retina through the electrode and a perception of a bright spot was formed in the patient's eye. Rizzo and Wyatt's group [33] have performed acute tests in six human subjects (5 RP patients and 1 normal vision subject as a control). Thin-film microelectrode arrays with a thickness of 10 μm and different diameters (50, 100, and 400 μm) were placed on the retina of subjects who were awake. Stimulation charges were delivered to the electrodes from an extraocular current source. This type of acute testing led to the design of the chronic retinal implants.

Second Sight and the Humayun group at USC have been continuously developing the intraocular retinal prosthesis since 1999. A large portion of this research and development for the first generation long-term retinal implant
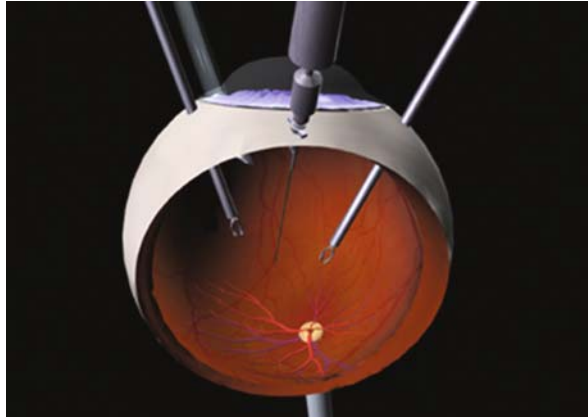
was done in collaboration with several universities funded by National Eye Institute (NEI). Between 2002 and 2004, the Humayun group has chronically implanted the Second Sight retinal prostheses in six blind subjects with retinitis pigmentosa [6].

The intraocular retinal prostheses implanted were the Argus[TM] 16 Retinal Implants – the devices developed based on existing cochlear implant technology of Advanced Bionics (Valencia, CA) with modified electronics, novel retinal electrode arrays, and novel video processing technologies. The Argus[TM] 16 device consists of a wearable external device and an implantable stimulator (Fig. 8).

Fig. 8 A schematic design of a retinal prosthesis with (A) camera in the glass frame; (B) wireless transmitter; (C) extraocular stimulator; and (D) intraocular electrode array (reproduced from Ref. [20] with permission from Elsevier)
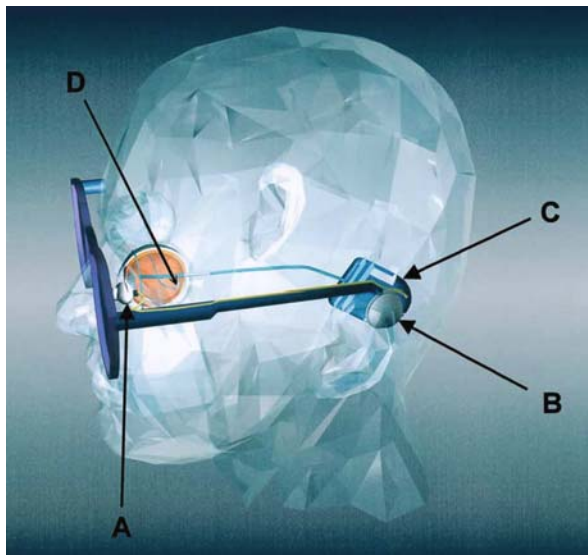
In this design, a small camera is housed in the glasses that connects to a belt-worn visual processing unit (VPU)[TM] (Fig. 9a). The VPU encodes visual information acquired from the camera and transmits electrical stimulation signals to the implanted unit. The data transfer is accomplished via a wireless inductive link using an external coil that is magnetically stabilized over the electronic implant. Personal computer-based custom software was also used to actively control the electrical stimulation command through the VPU.

Fig. 9 The Second Sight Argus 16 electrode retinal stimulator implant. (**a**). The Argus 16 external system consisting of a pair of glasses housing a camera, a hip worn visual processing unit (VPU), and a primary coil that is magnetically attached to the scalp just behind the ear (where a secondary coil in a stimulator is implanted). (**b**) The electronic stimulator is implanted in the bone behind the ear. The cable connecting the electronics package to the array is tunneled up into the orbit where it encircles the eye and enters through a pars planar incision. The array is fixed on the epiretinal surface with a metal tack

The Argus[TM] 16 implanted unit consists of an extraocular stimulator and an intraocular electrode array (Fig. 9b). The extraocular stimulator is surgically attached to the temporal area of the skull. A subcutaneous cable connected to the stimulator is used to deliver a charge across the eye wall to an intraocular electrode array placed on the retinal surface. The electrode array consists of 16 disc-shaped platinum electrodes in a square 4×4 layout embedded in silicone. Each electrode is approximately 500 μm in diameter. In some subjects, 250 μm electrodes or a combination of 250 μm and 500 μm electrodes were used. Edge-to-edge separation between two adjacent electrodes is approximately 200 μm [20].

Prior to introduction of the implant, the majority of the vitreous gel is removed. The electrode array is then positioned just temporal to the fovea on the top side of the retina near ganglion cells and a metal retinal tack was inserted through the electrode array and into the sclera. The threshold level of electrical stimulus charge remains below 0.35 mC/cm^2, which is an established long-term safety limit for platinum [34]. The timing of the pulse is typically a biphasic, cathodic first current pulse, 1 ms/phase with a 1 ms interphase delay [20]. The threshold currents to elicit the responses are considerably lower than previously reported acute tests [26]. Electrical stimulation produces phosphenes in the

human subjects. In general, the size and brightness of the phosphenes increase with higher stimulation current. The results are both reliable and reproducible with respect to the spatial location of the stimulating electrodes on the retina and the stimulating electrical current [6, 20]. In addition, the implanted devices with only 16 electrodes have enabled blind subjects to detect when lights are on or off, describe an object's motion, count distinct items, as well as locate and differentiate basic objects in an environment.

In early 2007, Second Sight received the FDA approval to conduct a clinical study of the Argus^{TM} II Retinal Prosthesis System. This smaller and higher resolution implant is the second generation of an electronic retinal implant. The Argus^{TM} II device has a thin-film array of 60 platinum electrodes that are attached to the epiretinal surface (Fig. 10). This phase I of a 3-year investigational device exemption (IDE) trial on blind RP subjects with four US centers, several European sites, and Mexico is underway. At the time of this writing, 18 subjects have been implanted. The development of retinal implant technology is supported by the National Eye Institute (NEI) of the National Institutes of Health (NIH), the Department of Energy's Office of Science (DOE) Artificial Retina Project, and National Science Foundation (NSF).
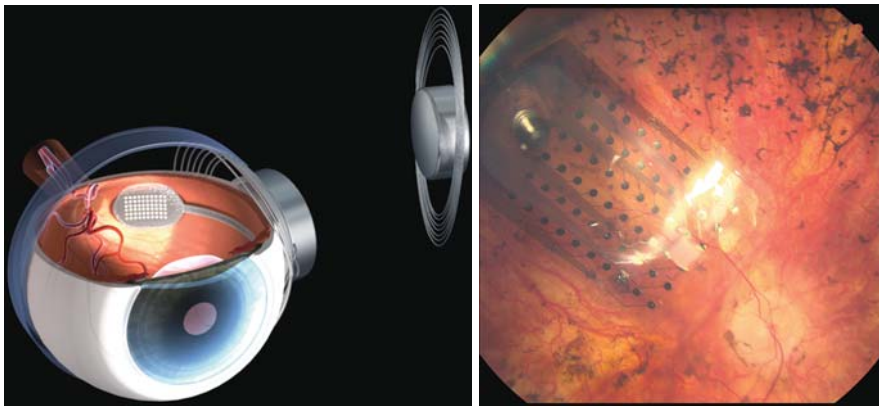
Fig. 10 *Left*: The second sight Argus II 60 electrode retinal stimulator implant. *Right*: A second sight thin-film 60 electrode array in the eye of a RP subject

Another industrial effort to develop epiretinal implants is Intelligent Medical Implants (IMI) AG (Zurich, Switzerland, and IIP Technologies AG – a subdivision in Bonn, Germany). The company's retinal implant has been implanted chronically in four blind RP subjects [35]. An epiretinal stimulator developed by IMI is shown in Fig. 11a [36]. An intraocular part of the implant is a thin-film polyimide array of 49 platinum electrodes (Fig. 11b). The array is placed in the macular area and fixed by a retinal tack with a silicone retainer ring. An extraocular part of the retinal stimulator is fixed onto the sclera.

Fig. 11 *Left*: An epiretinal stimulator developed by Intelligent Medical Implants (IMI) AG with a thin-film polyimide cable of gold tr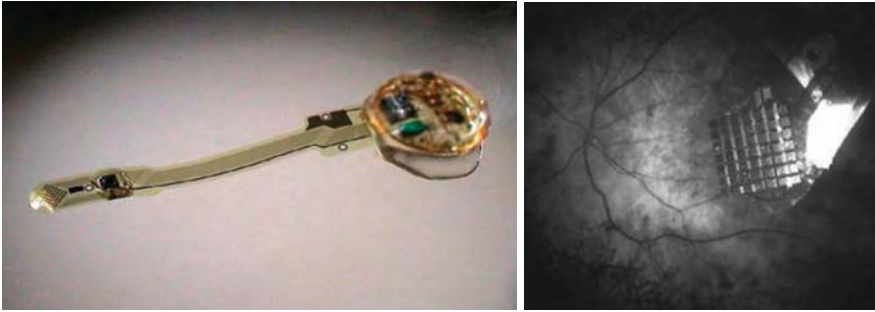aces. Reproduced from [36] with permission from Springer. *Right*: The electrode array has 49 platinum electrodes (reproduced from Ref. [37] with permission from Dr. G. Richard, University Eye Clinical Center, Hamburg, Germany)

Unlike the Second Sight implants in which both power and data are transferred through RF links, the power for the IMI retinal stimulator is provided through a RF link, while the stimulation data is transmitted via an optical link. The transmitters for both power and data are housed in a handheld unit. Based on the 9-month follow-up results, the implant is well tolerated in the eye. The subjects were able to distinguish between different points and recognize simple patterns such as horizontal bars [35].

3.3 Subretinal Implant

In the subretinal approach, photodiodes are implanted underneath the retina and used to generate currents that stimulate the retina. In Germany, a consortium led by Eberhart Zrenner [31] is being sponsored by the German government to develop subretinal implants. In the United States, Optobionics (Naperville, Illinois) is a private company founded in 2000 by the Chow brothers Alan and Vincent Chow, an ophthalmologist and an engineer, respectively, that had pursued the subretinal approach [8, 30] before filing for bankruptcy in 2007. The artificial silicon retina (ASR) microchip they developed is a 2-mm diameter silicon-based device that contains approximately 5000 microelectrode tipped microphotodiodes and is powered by incident light. Each pixel is 20×20 μm square and is fabricated with a 9×9 μm iridium oxide (IrOx) electrode electrochemically deposited to each pixel. Pixel current is 8–12 nA with approximately 800 foot-candles of illumination. In the pilot clinical trial for safety and efficacy studies reported in 2004, the ASR was implanted in six RP subjects from three centers.

The ASR microchip was placed within a fabricated Teflon sleeve and secured intraoperatively to a saline-filled syringe injector; it was then deposited within the subretinal space by fluid flow. From follow-up results ranging from 6 to 18

months, all ASRs functioned electrically with no implant rejection or retinal detachment. They reported that visual function improvements occurred in all subjects and included unexpected improvements in retinal areas distant from the implant. They claimed that the presence of the implanted ASR (either alone or coupled with low-level electrical stimulation) induced a "neurotrophic effect" or improved the visual function of the retina.

Optoelectronic subretinal implants rely on transformation of incident light to electrical signal via photodiodes. It is doubtful that current photodiodes are efficient enough to generate charges required to stimulate retinal cells. In fact, in vivo and in vitro studies indicated that a pure photovoltaic current was not sufficient to provide charge capacities for stimulating the bipolar cells [7, 38]. Additional energy inputs such as near-infrared radiation or RF power transmission are required [38, 39]. Powered subretinal implants using microelectrode arrays instead of microphotodiodes have been proposed by Zrenner [40] and the Harvard/MIT group [41].

A hybrid subretinal device with both microphotodiodes and microelectrodes has been developed by Retina Implant AG (Reutlingen, Germany) and Zrenner's team [40]. The device consists of an active chip ($3 \times 3 \times 0.1$ mm) with 1540 microphotodiodes and an additional 16 titanium nitride electrode (diameter 50 μm) array of 4×4 layout with a 280 μm intra-electrode space for direct stimulation powered externally (Fig. 12). Each microphotodiode cell has an area of 72×72 μm. When powered by a pulsed power supply at about 20 Hz with an active time per period about 500 μs, the cell delivers charge between 0.5 and 10 nC [42]. The maximum amplitude of the output pulses is set to 2 V to avoid exceeding the water window (see discussion in Section 4.4).

A polyimide carrier foil with 22 gold traces connects intraocular electrodes and photodiode chip to an extraocular connector which connects to a silicone cable (diameter 3 mm) with 22 coiled gold wires. This long cable of ~15 cm leads to an external plug behind a patient's ear for an external stimulator which
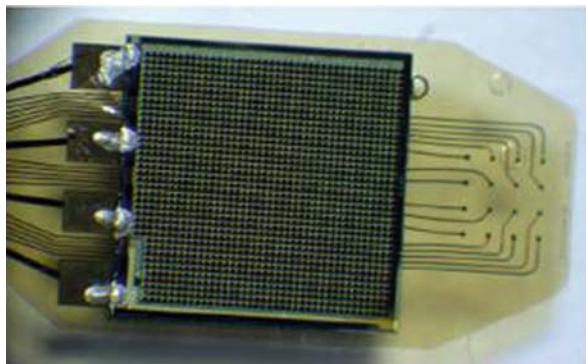

Fig. 12 A hybrid subretinal device with both microphotodiodes and microelectrodes developed by Retina Implant AG, Reutlingen, Germany (Couresy of Dr. Walter-Gerhard Wrobel, Retina Implant AG)

provides control signals, power, and stimuli. The devices have been successfully used in a 4-week clinical trial in seven blind RP subjects [43, 44]. Direct stimulation using electrodes approximately 1° apart produced phosphenes and subjects could recognize different spatial patterns, such as dots, lines, angles, or a square [40, 44].

It is critically important that visual stimulation electrodes are placed close to the target neuron cells to achieve low threshold charge and high resolution. Commonly this is achieved by using protruding or penetrating electrodes. Alternatively, neuron cells could be attracted to the electrodes. Daniel Palanker and co-workers [45, 46] at Stanford University, CA have designed a photo-diode-based subretinal implant with micro-channels that prompts migration of retinal cells into the proximity of stimulating electrodes. In vitro and in vivo experiments confirmed that the cells preserved axonal connections to the rest of the retina during migration and thus maintained the signal transduction path, but an integrated device has not yet been built. In a recent animal study by the same group [47], they compared three configurations (flat, pillars, and chambers) of passive subretinal arrays and found that three-dimensional pillars had minimal alteration of the inner retinal architecture (Fig. 13). In the micro-chamber design, encapsulation of cell bodies inside the chambers causes cell isolation and limits their access to diffusing metabolites, which may affect cells' long-term viability.
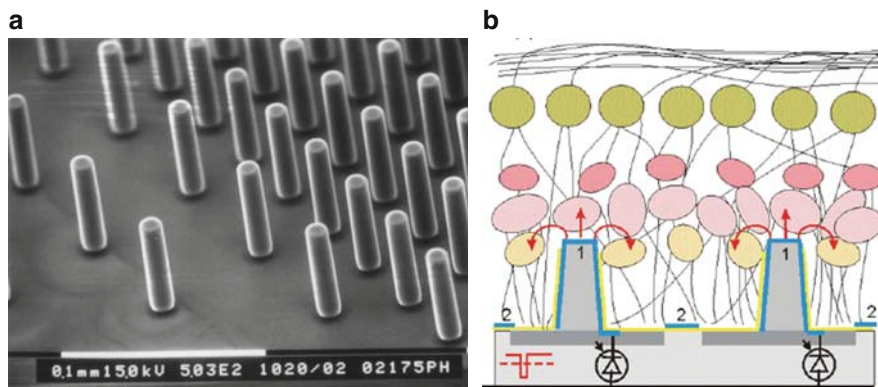

Fig. 13 (**a**) An SEM micrograph of the microfabricated SU-8 (an epoxy-based photosensitive polymer) pillar arrays. Each pillar is about 10 μm in diameter and 40–70 μm in height. (**b**) A pillar array may attract retinal cells to migrate into three-dimensional pillars in a subretinal implant for achieving intimate electrode-cell proximity (reproduced from Ref. [47] with permission from IOP Publishing Ltd)

Both epiretinal and subretinal approaches have advantages and disadvantages [7]. The epiretinal implants do not rely on the signal processing capability of the retina when stimulating the ganglion cells on the top of the retina [38].

Epiretinal implants are also significantly easier to safely surgically install when compared to subretinal implants. One theoretical advantage of the subretinal approach is that it may be able to take advantage of the complex processing circuitry of the retina by replacing the input signals from the photoreceptors with direct electrical input. However, recent data show that degeneration of the photoreceptors causes severe disorganization of the retinal circuitry [48], so stimulating with subretinal electrodes may result in a scrambling of the signal as it passes through the disordered circuitry.

3.4 Extraocular Implant

Chowdhury [49] studied the feasibility of using a retinal prosthesis for extraocular stimulation in anaesthetized adult cats. They found that electrodes placed on the exterior of the eye could reliably evoke visual cortex responses for a variety of configurations. Electrodes of Pt disks and Ag balls placed on the posterior scleral surface of the eye after a craniotomy and lateral orbital dissection. Cortical potentials evoked by electrical stimulation lower than 100 µA with single pulses were recorded at the primary visual cortex. These findings suggested that it is possible to electrically stimulate the retina with electrodes placed in an extraocular location, but thresholds are likely higher than for intraocular stimulation.

There is also a group from the Department of Ophthalmology at Osaka University in Japan that focuses on transretinal electrical stimulation [50]. They conducted acute electrophysiological experiments in rats. For electrical stimulation, a 0.2–0.3 mm in diameter silver-ball electrode was used as a stimulation electrode and an epoxy-coated stainless steel wire 0.2 mm in diameter was used as a return or reference electrode. The Ag-ball electrode was inserted into a small lamellar scleral resection made at a short distance from the optic nerve in the upper temporal part of the sclera. The stainless steel return electrode with about 2 mm of the tip exposed was inserted approximately 4 mm into the vitreous. In most stimulation experiments, the return electrode in the vitreous was used as the cathode. A single monophasic pulse of electrical current ranging from 5 to 300 µA was applied between these two electrodes for various pulse widths of 0.05, 0.2, or 0.5 ms.

The electrically evoked potentials (EEPs) from transretinal stimulation were recorded from the superior colliculus (SC) in rats. A silver-ball recording electrode (Ag/AgCl, 0.2–0.3 mm in diameter) was positioned on the exposed SC surface by a three-dimensional micromanipulator. A stainless steel screw was implanted into the occipital bone approximately 1 mm behind the lambda and used as a reference electrode for recording. EEP recordings confirmed that transretinal electrical stimulation did generate focal excitation in retinal ganglion cells in normal animals and in those with degenerated photoreceptors. Since the study was acute, long-term effects of retina or choroid damages could not be accessed.

A similar approach was used by Sung June Kim's group at Seoul National University, Korea for suprachoroidal stimulation [51, 52]. The prototype implant, which was built based on a cochlear implant, has two unique features (Fig. 14). Rather than inserting a reference electrode into the vitreous as in Tano's approach [50], they placed the reference electrode on the outer scleral surface without penetrating the vitreous cavity. This design will simplify surgical procedures and reduce possible ocular damage from penetrating the vitreous cavity.

Fig. 14 A suprachoroidal (extraocular) implant for transretinal stimulation. The device consists of a receiver coil, hermetically sealed titanium package, and polyimide-based gold stimulation and reference electrodes (reproduced from Ref. [52])

The second feature was that the implant was powered by a small rechargeable battery so that the external components, such as power supply and data control parts, could be removed during a chronic stimulation experiment. Transfer of data and charging the batteries were accomplished through inductive links. The power consumption determined on a dummy resistor of 1.3 kΩ was around 2 mW at 520 μA, 1 ms, and 4 Hz biphasic current. Under these conditions, the battery could supply the power to the stimulator for over 30 h. The rechargeable battery with a capacity of 75 mAh (4.2 V) in the implant could be fully recharged within 3 h with 25 mA charging current through a RF inductive link.

The 7 channel stimulator developed by Kim's group was hermetically packed in a titanium case. The feedthroughs connected the electrode array and receiver coil to the retinal stimulator. A ceramic sintering process was used to fix the feedthroughs in the ceramic plate that provided electrical isolation. Brazing and laser welding techniques were employed to achieve hermetic sealing of the titanium housing [52, 53]. The electrode array has an integrated stimulation electrode array and a large reference electrode. The seven stimulation electrodes have an exposed strip-shaped area of 750×300 μm that is arranged in a 4 mm × 4 mm area. The reference electrode, also made of polyimide insulated thin-film gold, has a diameter of 1.5 mm. The electrodes have typical impedances of 1.3 kΩ and 300 Ω in PBS at 1 kHz for the stimulation and reference electrode, respectively.

Surgical implantation into rabbits was performed to verify the functionality and safety of this newly designed system. A polyimide-based gold electrode array was implanted in the suprachoroidal space. EEPs were recorded via stainless steel needle electrodes from the cortex during electrical stimulation of the retina. They found that the placement of the reference electrode in the