Retinal prostheses: current challenges and future outlook

JESSICA O. WINTER 1,2,3,*, STUART F. COGAN 4 and JOSEPH F. RIZZO III 1,5

1 Center for Innovative Visual Rehabilitation, VA Medical Center, Boston, MA, USA
2 Department of Chemical and Biomolecular Engineering, The Ohio State University, 140 West 19th Avenue, Columbus, OH 43210, USA
3 Department of Biomedical Engineering, The Ohio State University, 140 West 19th Avenue, Columbus, OH 43210, USA
4 EIC Laboratories, Norwood, MA, USA
5 Department of Ophthalmology, Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, MA, USA

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Abstract—Blindness from retinal diseases, including age-related macular degeneration (AMD) and retinitis pigmentosa (RP), usually causes a significant decline in quality of life for affected patients. Currently there is no cure for these conditions. However, over the last decade, several groups have been developing retinal prostheses which hopefully will provide some degree of improved visual function to these patients. Several such devices are now in clinical trials. Unfortunately, the possibility of electrode or tissue damage limits excitation schemes to those that may be employed with electrodes that have relatively low charge densities. Further, the excitation thresholds that have been required to achieve vision to date, in general, are relatively high. This may result in part from poor apposition between neurons and the stimulating electrodes and is confounded by the effects of the photoreceptor loss, which initiates other pathology in the surviving retinal tissue. The combination of these and other factors imposes a restriction on the pixel density that can be used for devices that actively deliver electrical stimulation to the retina. The resultant use of devices with relatively low pixel densities presumably will limit the degree of visual resolution that can be obtained with these devices. Further increases in pixel density, and therefore increased visual acuity, will necessitate either improved electrode-tissue biocompatibility or lower stimulation thresholds. To meet this challenge, innovations in materials and devices have been proposed. Here, we review the types of retinal prostheses investigated, the extent of their current biocompatibility and future improvements designed to surmount these limitations.

Key words: Visual prosthesis; retina; biocompatibility; electrode.

*To whom correspondence should be addressed. E-mail: winter.63@osu.edu
INTRODUCTION

Recent estimates indicate that over 937,000 Americans suffer profound vision loss, while an additional 2.4 million display some degree of visual impairment [1]. A direct link between decreased visual acuity and age has been established, with up to 12% of individuals over age 80 being affected by low vision, usually as a result of age-related macular degeneration (AMD) [2]. As the US population continues to age, it is likely that the total number of affected individuals will increase, perhaps up to 50% by 2020 [3]. AMD, and other forms of neural blindness, cannot be treated by any available means. Numerous strategies are being tried to treat neural blindness, including: transplantation of retinal neurons, retinal pigment epithelium or stem cells, molecular genetic repair and retinal prostheses. Retinal [4–8], cortical [9, 10] and optic nerve [11, 12] visual prostheses use microfabricated electronic components to stimulate neural circuitry that is still available despite whatever neural damage has caused blindness. This approach is attractive in that prostheses can directly stimulate surviving nerve cells and does not require the implant to establish proper neural connections with the host tissue. Additionally, devices with an analogous purpose have proven to be enormously successful in restoring hearing to the deaf [13]. However, despite decades of research [14–25], visual prostheses have not advanced beyond early clinical trials and have not yet produced a level of vision that has been demonstrated to improve the ability of patients to perform visual tasks related to daily activities.

The reasons for slow development of visual prosthetic devices are numerous. Among these is the fact that visual prostheses will almost certainly have to have a moderately large number of stimulating electrodes to have any hope of providing detailed visual perception. However, simply having a relatively large number of electrodes does not guarantee that the nerve tissue can be stimulated in a way that would faithfully transmit impulses (via electrical fields) that would correspond to the intended pattern of stimulation based upon the visual scene. Although cochlear implants can produce hearing with as few as 8 electrodes [13], visual prostheses have not enjoyed the same success. The purpose of this review is to identify some of the challenges facing the development of high pixel density visual prostheses. Differences in the various visual prostheses under investigation are discussed in this context, and future directions for overcoming these challenges and improving the performance of the prostheses are suggested.

RESTORING VISUAL FUNCTION

Physiological visual processing

In a healthy individual, vision begins when the lens focuses light entering the eye onto the retina (Fig. 1) [26]. At the level of the photoreceptors, the incoming light rays are detected by some fraction of the about 190 million photoreceptors (i.e., rods and cones). The photoreceptors are not distributed evenly; there is a substantially
Figure 1. Retinal anatomy and retinal prosthesis implant locations. The retina consists of several organized layers of cells and tissue. In normally sighted individuals, light impinging on the retina is received by photoreceptors (lower left), which convert light into an electrical signal. That signal is processed by the bipolar and ganglion cells, and transmitted to the brain. Nutrients to the retina are supplied by the retinal pigment epithelium (RPE) and the choroid, a dense network of blood vessels. Epi-retinal implants are designed to interact with the retina from the vitreous side and are in closest proximity to ganglion cells. Sub-retinal implants would be placed between the retina and the choroid, in the place normally occupied by photoreceptors. This figure is published in colour at http://www.ingenta.com
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greater density of photoreceptors within the central retina (i.e., macula). Capture of light rays by photoreceptors causes a hyperpolarization of these cells, which reduces the release of neurotransmitter at their synaptic terminals. This generates a graded electrical signal at the level of the inner nuclear layer, which is transmitted through bipolar cells to the retinal ganglion cells (RGC). Within the inner retina where RGCs reside, the graded electrical signal is converted into a series of electrical spikes, known as action potentials. Axonal extensions from the RGCs, the only output cells from the eye, form the optic nerve, which transmits the electrical signals related to visual input to the brain. The signal is transmitted along the RGC axons until it reaches the lateral geniculate nucleus (LGN), where the axons synapse. The final relay along this retinocortical visual pathway begins at the LGN and extends to the primary visual cortex. From here, the information is passed forward to numerous “higher cortical” visual pathways. Visual perception is created by the collective activity of these widely-distributed visual cortical regions.

Vision loss can occur from deficits at any stage in the vision processing system. Retinal and optic nerve prostheses are designed to treat diseases of the retina, primarily retinitis pigmentosa (RP, which accounts for 5% of cases of neural visual loss among younger Caucasian patients within the industrialized world [27]) and age-related macular degeneration (AMD, which accounts for 47% of visual loss among older Caucasian patients within the industrialized world [27]). Cortical prostheses could theoretically address these conditions plus those that occur because of damage further along the retinocortical visual pathway. A cortical prosthesis could provide visual assistance to patients with glaucoma (which accounts for 29% of cases of visual loss among older Caucasian patients [27]) and diabetic retinopathy (which accounts for 8% of cases of visual loss among older Caucasian patients [27]). The requirements for device resolution will likely vary for each type of disease and also differ from one patient to another with the same disease. For example, RP may eventually result in no light perception, thus a low resolution device can improve patient quality of life; whereas AMD patients typically retain normal vision in the periphery. A resolution of 20/200–20/400 [28, 29] is the generally accepted goal for visual acuity for this patient group, but only clinical tests can reveal the true threshold for patient acceptance.

Clinical results related to the development of retinal prostheses

The concept of prosthetic vision is simple; electronic components are used to convert light into an electrical signal that stimulates neurons in the visual pathway. The neural signal is then processed by the brain to generate phosphenes (i.e., flashes of light). In practice, the realization of prosthetic vision has proven complex and challenging. Two basic types of retinal prosthetic devices have evolved. The most straightforward type of device consists of a multiphotodiode array (MPDA) implanted in the sub-retinal space (i.e., between the retinal pigment epithelium and the retina, Fig. 1). However, this type of device has a very limited electrical output, which is arguably insufficient to drive retinal neurons (see below),
especially diseased neurons that have higher-than-normal activation thresholds as a consequence of a retinal degeneration. However, it would be possible to provide supplemental electrical power to implanted MPDAs by including additional hardware in the system design.

**MPDA devices.** Sub-retinal MPDAs were first proposed in 1956 by Tassiker [14], who envisioned a selenium photodiode that would provide stimulation to the retina. More recently, sub-retinal MPDAs have been studied by two independent groups: German Southern Consortium/Retinal Implant (Reutlingen, Germany) [6] and Optobionics (Chicago, IL, USA) [4]. MPDAs convert light impinging on the retina into an electrical signal, which is received by the cells of the inner retina. MPDAs possess several advantages over other types of retinal implants. MPDA devices and other sub-retinal implants provide functional replacement at the earliest possible level, substituting for damaged photoreceptors. MPDA power is provided by incident light, reducing the number of external and implanted electronic components. Also, little signal processing is needed because sub-retinal devices replace the first component in the visual cascade.

However, practical implementation has proved difficult. Incident light does not appear to provide sufficient power to drive the devices [30, 31], requiring the addition of external power components. Devices without external power components have been used in clinical trials sponsored by Optobionics [4]. Ten patients with retinitis pigmentosa have been implanted to date; testing has reportedly produced visual images, including in areas of the visual field that were not being directly driven by the implant [32]. Although the exact increase in visual acuity is not described and varied across patients, visual improvement has apparently persisted over 3.5 years with only a small decline in quality over time [4, 33]. However, the evidence of success is far from conclusive. Much of the reported success is based on subjective patient reports. Similar sub-retinal MPDA devices, but with additional supplemental power, have also been chronically implanted in four patients by Retinal Implant.

**MEA devices.** MEAs consist of planar microelectrode arrays connected to an implantable signal processor (Fig. 2). In one configuration, visual images are collected with a digital camera and interpreted by the signal processor, which develops and transmits a stimulation pattern to the electrodes. MEAs have been investigated at a number of implant sites, including the retina, optic nerve and visual cortex, each requiring varying levels of upstream signal processing that must be replicated. Retinal devices based on this platform have been developed by three groups: USC/Second Sight (Sylmar, CA, USA) [8], Intelligent Medical Implants (Bonn, Germany) [7], which evolved from the Northern German Consortium, and our group, the Harvard Medical School/Massachusetts Institute of Technology/Veterans Administration consortium (Boston, MA, USA) [5]. The Second Sight and Intelligent Medical Implant devices target epi-retinal implant locations, whereas the Harvard/MIT/VA
Figure 2. (Left) Artist’s conception of CIVR, sub-retinal prosthesis. The image obtained by an external camera is translated into an electromagnetic signal that is transmitted wirelessly to the implanted secondary data coil attached to eye. Power is transmitted similarly. Essentially the entire volume of the implant lies outside the eye. (Right) This perspective reveals that only the electrode array (arrow) penetrates the wall of the eye. This figure is published in colour at http://www.ingenta.com

device targets a sub-retinal implant location. Although there is substantial disagreement, there may be some benefit of the sub-retinal implant location in lower electrical thresholds [6, 34–38].

Epi-retinal devices have been implanted by USC/Second Sight in three patients with retinitis pigmentosa and showed no overt signs of toxicity for up to 21 months [8, 39, 40]. The devices have generated phosphenes and have allowed repeated determinations of perceptual thresholds [41]. Their subjects were able to discriminate between two objects and in some cases observe object movement [42, 43]. Implantation of these devices in animals has been shown to drive the pupillary light reflex [44] and to cause suppression of plasma melatonin, which is under the control of a retino-hypothalamic pathway that subserves circadian rhythms [45]. The implanted devices to date have contained roughly 16 functional electrodes, which would at best seemingly provide only relatively coarse vision, perhaps in the range of 20:1200 [29, 46].

Device resolution

Among devices currently in clinical trials, the MPDA devices have the smallest electrode sizes (approximately 20 µm diameter). However, electrodes of this size, powered by ambient light, are unlikely to provide sufficient charge to reach threshold for neural excitation [30, 31]. The devices that have reportedly provided the best vision for patients have employed approximately 20 electrodes with diameters of approximately 500 µm [8, 29, 46]. Given that most neuronal cell diameters are approximately 10 µm within the central retina, there is a relatively high ratio of neurons to stimulating electrodes, which would presumably degrade the specificity and spatial resolution of any induced images. The technology to create smaller, more numerous electrodes certainly exists [47], but safety concerns (see section on Effects of electrical stimulation on the electrode–tissue interface), electrical cross-talk [48] and power requirements [48] have limited prostheses to a
small number of large electrodes. Of these, safety concerns are the major limiting factor on electrode size. Additionally, at this point in development, it is not clear that having access to a larger number of stimulating electrodes would necessarily translate into being able to improve the quality of induced visual percepts.

Estimates of the number of electrodes that would be required to yield various levels of visual acuity with a retinal prosthesis have been studied by several groups. These studies have provided estimates that range between 256 and 625 electrodes, which theoretically might yield best visual acuity of 20/420 and 20/30, respectively [49–51]. However, the number of electrodes required depends on the ability of electrode materials to safely transmit charge and also on the proximity of the target tissue to those electrodes (Fig. 3) [29].

CHALLENGES TO ACHIEVING USEFUL VISION

The barriers in restoring vision to the blind are substantial. In addition to the usual biomaterial issues such as toxicity, tissue encapsulation and cellular/immune responses that might be incited by the foreign materials, an electrical prosthesis must also provide long-term stability of the metal electrodes while minimizing any tissue damage that occurs as a result of the electrical stimulation. Induced tissue damage will reduce the excitability of the tissue and limit the potential for vision restoration.

At the electrode–tissue interface, electrochemical reactions and heat production generally accompany charge injection. These factors constrain maximum charge injection levels and stimulation electrode area, which ultimately constrains the
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spatial resolution that could be achieved by electrical stimulation. The potential biocompatibility and long-term functional stability of a retinal prosthesis are further complicated by ongoing anatomical and physiological changes that inevitably occur within the retina in patients with retinitis pigmentosa [52], which is the primary disease that we hope to treat in the early years of visual prosthetic implantations. To develop a clinically viable implant, these concerns must be satisfactorily addressed over time scales of 10 years or more following implantation. Much work has been done to explore these issues; however, there remains a notable absence of knowledge in key areas, including perceptual thresholds, tissue damage thresholds and the impact of disease progression on the potential for vision restoration.

Charge thresholds for vision perception

One of the most critical needs in the development of visual prostheses is a determination of the stimulation threshold that is required to produce a visual percept (usually measured as charge/phase during current pulsing). The amount of charge required to reach threshold is at least a function of the pulse duration, pulse strength and the particular waveform applied [53]. As pulse duration decreases, the current required to solicit a response increases dramatically. However, at long pulse durations, the stimulation threshold approaches a constant value, known as the rheobase. Electrical thresholds for eliciting a perceptual response in the human have been measured during acute (i.e., hours-long) and chronic studies with electrodes implanted either on the retina, the optic nerve, the surface of the visual cortex, or intracortically, within the visual cortex (Table 1).

The data in Table 1 reveal marked differences in thresholds between healthy patients and those who are blind because of retinal disease, which includes all of the diseased citations except those by Hambrecht who reports on a patient with Table 1.

Comparison of human visual perceptual thresholds and corresponding waveforms for retinal, optic nerve and cortical stimulation

<table>
<thead>
<tr>
<th>Placement</th>
<th>Type</th>
<th>Charge/phase (µC/ph)</th>
<th>Charge density (µC/cm²)</th>
<th>Sight</th>
<th>Waveform</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.2–1.8</td>
<td>1630–14 680</td>
<td>RP/AMD</td>
<td>PW ≤ 2 ms, 1 Hz</td>
<td>[54]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.1–5.5</td>
<td>160–70 000</td>
<td>RP/AMD</td>
<td>PW ≤ 4 ms, ≤10 Hz</td>
<td>[20]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.33–1.9</td>
<td>320–12 230</td>
<td>RP/AMD</td>
<td>PW 0.25–16 ms, 20 Hz</td>
<td>[25]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.024–0.1</td>
<td>80–306</td>
<td>Normal</td>
<td>PW 2 ms, 20 Hz</td>
<td>[25]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.13</td>
<td>NA</td>
<td>RP</td>
<td>PW 1 ms</td>
<td>[55]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.05–0.5</td>
<td>24–240</td>
<td>RP</td>
<td>PW 1 ms</td>
<td>[8]</td>
</tr>
<tr>
<td>Epi-retinal</td>
<td>Surface</td>
<td>0.006–1.12</td>
<td>5–570</td>
<td>RP</td>
<td>PW 1 ms</td>
<td>[56]</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Surface</td>
<td>0.0070–0.124</td>
<td>4–62</td>
<td>RP</td>
<td>PW 25–400 µs, 0–160 Hz</td>
<td>[57]</td>
</tr>
<tr>
<td>Intracortical</td>
<td>Penetrating</td>
<td>0.0004–0.0046</td>
<td>190–2300</td>
<td>Glaucoma</td>
<td>PW = 200 µs, 200 Hz</td>
<td>[58]</td>
</tr>
<tr>
<td>Intracortical</td>
<td>Penetrating</td>
<td>0.004</td>
<td>2000</td>
<td>Normal</td>
<td>PW = 200 µs, 100 Hz</td>
<td>[58]</td>
</tr>
<tr>
<td>Cortical</td>
<td>Surface</td>
<td>200</td>
<td>11</td>
<td>Normal</td>
<td>PW = 200 µs, 100 Hz</td>
<td>[58]</td>
</tr>
</tbody>
</table>

NA = not available.
glaucomatous optic neuropathy. Rizzo et al. [5] observed charge/phase thresholds for the normal retina that are four times less than the lowest threshold observed in the RP retina. Interestingly, despite significant degeneration of the retinal ganglion cells that form the optic nerve, perceptual thresholds of optic nerve stimulation in RP patients are similar to those of normal patients [57]. This finding differs from those of groups stimulating what are presumably the same axons at an epi-retinal location.

Higher thresholds in diseased versus healthy retina have also been measured in experiments using stimulating electrodes placed on the surface of the eyeball [59]. It is possible that stimulation thresholds will increase progressively as the disease process advances, which might require the use of adjustable stimulation parameters. Examination of epi-retinal thresholds obtained by Rizzo et al. [5], Weiland et al. [55], Humayun et al. [8] and Mahadevappa et al. [56], excluding data from normally-sighted patients, reveals an average mid-range value of the perceptual threshold in the diseased retina of approximately 0.5 µC/phase.

Causes of high perceptual threshold

The causes of high perceptual thresholds are not known but presumably relate to several factors. Some likely explanations include: the anatomical and physiological changes that accompany retinal degeneration; lack of understanding about the preferred methods of applying electrical stimulation; use of relatively large stimulating electrodes that might create large inhibitory electrical fields; and the challenge for the brain to learn how to make use of this new information that is being generated by such artificial means. Some plausible factors that might be relevant also include: formation of scar tissue on or around the stimulating electrodes, and the difficulty in achieving intimate electrode–nerve contact. Mitigating any of these factors could lead to significant advances in prosthesis resolution.

Device biocompatibility: gliosis. In general, the gross biocompatibility of implanted devices has been good. Tissue reactions to implantation in general seem not to be destructive. There is, for instance, a lack of any real encapsulation of the foreign material [60, 61], which we (reasonably) expected to see. There is some degree of “immune privilege” enjoyed by the eye, which might account for some of these favorable outcomes [62, 63]. Furthermore, when an inflammatory reaction does occur, it is typically related to the trauma of surgical implantation.

The field has collectively produced evidence of uneventful placement of a variety of foreign materials at the levels of the retina [64, 65] and optic nerve [66] for up to 4 years. However, some studies have shown up-regulation of glial fibrillary acidic protein (GFAP) in the Müller cells of the retina. In addition, in the case of sub-retinal implants, there has always been some degeneration of photoreceptors with chronic sub-retinal implantation, given that the blood circulation of the choriocapillaris, which is beneath the retina, is required to sustain the health of photoreceptors. The photoreceptors also depend upon an integral anatomical
relationship with the retinal pigment epithelium, which also underlies the retina [67–70]. There is also undoubtedly some degree of trauma to the outer retina when a sub-retinal implant is performed.

Although it has not been explicitly observed in the retina, gliosis is also expected to occur. Persistent gliosis has been observed with CNS microelectrodes, accompanied by a loss of neuronal cells [71]. Although the gliosis is localized to within 50–100 µm of the implant, this spatial extent is sufficient to interfere with the neural recording and, probably, the stimulation capabilities of the electrodes. Minimizing gliosis at the electrode-neural interface would presumably improve device performance. Certain types of scar tissue increase electrical resistance to current flow [72]. Additionally, accumulation of scar tissue can expand the separation between electrodes and target cells. Both factors increase the power required to achieve threshold levels of charge injection. However, scar tissue can also have a beneficial effect, by securing the implant to the target site, which may be especially useful for epi-retinal implants [73].

**Neuron–electrode interfacing.** A significant contributing factor to high patient thresholds is the proximity of the device to target cell populations. In many cases, it is not possible to situate the implant near cells of interest. For example, in dogs, epi-retinal arrays designed to rest on the retina surface actually displayed a mean distance of 20–50 µm from the retina [74]. These arrays targeted retinal ganglion or bipolar cell bodies located beyond the inner limiting membrane and nerve fiber layer (approximately 100–200 µm thick [75]). Given that activation thresholds increase significantly with distance from the retina [54, 76], these separations can substantially elevate thresholds over those measured in vitro.

Increased electrode separation also decreases the likelihood that specific cell classes or relatively small collections of neurons could be driven by electrical stimulation. There was original speculation [47] and later in vivo evidence that axons of retinal ganglion cells are driven by electrical stimulation applied to the epi-retinal surface [77], although patients almost never report visual percepts that might be reasonably ascribed to axonal stimulation. Perhaps an effect of decreased specificity of excitation may simply be the generation of “noise” during neuronal signal processing, which might compromise perceptual resolution. These issues are not limited to retinal devices. For example, one version of the optic nerve prosthesis consists of only 4 electrodes, and highly selective excitation of interior axons would not be possible with such limited hardware [78]. Currently, the clinical [20] and theoretical [79, 80] evidence seems to suggest that limited selective excitation of cell bodies may be possible, but further in vivo study is required.

**Effects of electrical stimulation on the electrode–tissue interface**

Electrical stimulation of nerve requires charge injection across the electrode–tissue interface, which exposes tissue to electrical current and any products of the electrochemical reactions at the interface. The effects can have wide-reaching
consequences on the tissue and the device. Excessive levels of charge may damage tissue [81], the electrode [82, 83] and, in some instances, suppress the electrical excitability of neuronal tissue even in the absence of histologically apparent damage [84–86]. The need to employ stimulation charge densities that are believed to be acceptable (<100–200 µC/cm² for platinum electrodes) has mandated the use of relatively large electrodes for retinal prosthetic devices. The large electrodes employed have not produced any definable histological damage [87], but may be limiting the visual resolution of the devices that have been implanted.

Charge-injection waveforms and limits. Electrical stimulation initiates a functional response by depolarizing membrane potentials in excitable tissue. Depolarization is achieved by the flow of ionic current between two or more electrodes, one of which is usually in fairly close proximity to the target tissue. Charge-injection for neural stimulation is typically applied in the form of rectangular current pulses, with each pulse having cathodal and anodal components possessing current amplitudes and durations that result in an overall zero net charge (i.e., charge-balance) for the pulse. A typical pulse waveform with pulse parameters is provided in Fig. 4.

The majority of electrodes are metallic conductors and reactions at the electrode-tissue interface are required to mediate the transition from electron flow in the metal to ion flow in the tissue. These reactions are both capacitive, charging and discharging the electrolyte double-layer, and Faradaic, in which surface-confined species are reversibly oxidized and reduced. The maximum charge that an electrode can inject into tissue without irreversible reactions is termed the “safe charge-injection limit”. This limit is usually defined as the amount of charge that can be injected without polarizing the electrode beyond the potential limits for reduction or oxidation of water. This limit is based on the premise that irreversible reactions will produce toxic by-products that damage tissue near the electrode. Charge injection limits depend on the current density, which is a direct measure of the rate of the

Figure 4. A biphasic, charge-balanced current pulse typical of those used in neural stimulation. For charge balance, \( I_c \times t_c = I_a \times t_a \). The parameters and normal range for each value are: \( I_c \), cathodic current (1 µA–10 mA); \( I_a \), anodic current (1 µA–10 mA); \( t_c \), cathodic half-phase period (50 µs–10 ms); \( t_d \), interphase dwell (0–1 ms); \( t_a \), anodic half-phase period (50 µs–10 ms); frequency (not shown), pulses per second (10–250 Hz).
double-layer charging and reduction-oxidation processes, the pulse frequency and the relative magnitudes of $I_c$ and $I_a$. The geometry and porosity of the electrode also impact the uniformity and magnitude of the polarization [88, 89].

Electrode corrosion. In addition to avoiding tissue damage, it is also desirable to avoid reactions that can lead to electrode dissolution, or corrosion. In the absence of an imposed stimulus pulse, all materials presently used as stimulation electrodes resist corrosion when implanted into the body. However, during charge injection an electrode may be polarized to a potential at which irreversible degradation in the form of electrode dissolution or delamination of electrode coatings occurs. The potential for and the severity of corrosion depends on many factors including the quantity of charge delivered, the rate of charge delivery (i.e., current density), the shape of the pulse waveform, and the strategy used to balance the cathodal and anodal charges in the pulse. Even when stimulus pulses are delivered with charge-balanced waveforms, electrode degradation can occur.

For example, intracortical microelectrodes coated with activated iridium oxide (AIROF) were severely damaged by polarization more negative than about $-0.6 \text{ V (vs. Ag|AgCl)}$ when pulsed in cat cortex [83]. The AIROF coatings delaminated from the electrode and were deposited into the tissue around the tip of the microelectrode. Platinum and PtIr-alloys, which are the most commonly used electrode materials for implantable devices, exhibit some dissolution in vitro even at very low levels of charge-injection (20–50 $\mu\text{C/cm}^2$) [90, 91]. Other in vitro studies have shown that the presence of protein greatly reduces the dissolution rate, so in vivo dissolution is likely to be less than that revealed by in vitro studies, especially when performed in inorganic media [92]. Nonetheless, corrosion has occurred in vivo with Pt electrodes in as little as 3 years of use in a cochlear implant, and Pt was found in tissue around surface cortical electrodes pulsed at 100 $\mu\text{C/cm}^2$ after pulsing for only 36 h [90, 93]. In the cortical surface electrode study by Robblee et al. [90], the rate of Pt dissolution decreased over 36 h of pulsing and very low dissolution rates for Pt electrodes may be expected at approximately 100 $\mu\text{C/cm}^2$ once the electrode–tissue interface has stabilized.

The preferred list of candidate electrode materials for a visual prosthesis includes Pt, PtIr-alloys, iridium oxide and titanium nitride. Platinum electrodes have been used for epi-retinal stimulation studies by Humayun et al. [20, 54] and Mahahdevappa et al. [56]. Activated iridium oxide electrodes have been used by Rizzo et al. [5, 25] in epi-retinal studies and sputtered iridium oxide has been used by Chow et al. [70] in sub-retinal photodiode arrays. Titanium nitride electrodes have been used by Zrenner et al. [69] in studies of sub-retinal microphotodiode stimulation of degenerated rat retina. Interestingly, even in the absence of imposed currents, the titanium nitride was poorly biocompatible compared with iridium, SiO$_2$ or Si$_3$N$_4$, as judged by retinal neuron cell survival in disassociated cell cultures. The charge-injection capacities of these materials have been evaluated in vitro by several investigators and the range of values is
presented in Table 1. Activated iridium oxide has the highest reported charge-injection capacity. However, the measured capacities can vary greatly with the thickness, morphology and preparation method of an electrode surface or coating; the values in Table 2 are specific to those features of the electrodes used in the studies reported.

**Electrical-stimulation-induced tissue damage.** Although tissue damage is possible from the accumulation of toxic products from irreversible reactions at the electrode, not all tissue damage is the result of such electrochemical reactions. For instance, a comparison of Faradaic and capacitive electrodes pulsed with charge densities of 80–100 µC/cm² for 7 h showed equivalent tissue damage [97]. The cause of this type of tissue damage, which is manifested as tissue necrosis, vacuole formation and disruption of the plasma membranes (Fig. 5), is not known [98, 99]. One hypothesis is that damage occurs as a result of excessive neuronal

<table>
<thead>
<tr>
<th>Material</th>
<th>Charge limit (mC/cm²)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt and PtIr-alloys</td>
<td>0.05–0.15</td>
<td>[91]</td>
</tr>
<tr>
<td>Iridium oxide</td>
<td>1–3.5</td>
<td>[94, 95]</td>
</tr>
<tr>
<td>Titanium nitride</td>
<td>approximately 1</td>
<td>[96]</td>
</tr>
</tbody>
</table>

**Figure 5.** Nissl-stained tissue sections of cat cortex exposed to (A) an unpulsed microelectrode and (B) a microelectrode pulsed at 60 nC per phase for 7 h. The microelectrode track is indicated with (T). Neurons near the unpulsed electrode appear as ovoid entities with small spot(s) (nucleoli). In most cases, these are accompanied by smaller, darkly-stained satellite cells (oligodendrocytes). Near the pulsed electrode, the damage from the stimulation is manifested as a loss most of the neurons within 50 µm of the electrode and by an aggregate of inflammatory cells (darkly-stained, globular entities) around the electrode site. From their morphology, these cells are most likely macrophages phagocytosing remnants of cells or cellular processes damaged by the electrical stimulation. Macrophages originate from blood vessels and a number of them can be seen closely surrounding the large blood vessel at the upper right (“perivascular cuffing”). This figure is published in colour at http://www.ingenta.com
firing, which can increase neurotransmitter release and subsequent Ca$^{2+}$ uptake that leads to cell death [85]. Another possibility is that the imbalance between normal and excitation-induced intracellular concentrations of K$^+$ and Na$^+$ may produce cellular edema that leads to cell damage. Finally, high stimulus currents have been linked to a breakdown of the blood-brain barrier [100], and it is possible that an increased number of immune cells enter the tissue and incite tissue damage.

Damage increases with charge density [81, 84] and charge per phase [76, 100]. In fact, when histological results of stimulation studies are plotted on a charge per phase versus charge density graph (Fig. 6, black and white circles representing damaging and non-damaging stimulation, respectively), a damage threshold can be estimated. An approximate boundary between damaging and safe thresholds is identified by the dashed line in Fig. 6, which is derived from the tissue-damage model proposed by Shannon [101], for which we have selected $k = 1.85$ to match the histologically observed boundary. Above the $k = 1.85$ line, damage occurs, while below the line damage is not seen [81, 84]. The model considers surface electrodes in sufficiently close proximity to the excitable tissue that elevated, non-uniform current distributions at the edges of the electrodes are the primary cause of tissue damage. This geometry is similar to that encountered with the planar, circular electrodes employed in the epi-retinal studies reported in Table 1, and should be applicable to either epi-retinal or sub-retinal placements when planar electrodes are

![Figure 6. A comparison of electrical thresholds for perception in human volunteers using epi-retinal stimulation in four acute and two chronic studies [8, 56]. Thresholds for Humayun [8, 56] are 10 weeks post-implant. Included are data and model predictions for tissue damage. The data points from Rizzo et al. [25] marked with * are from a normally seeing subject. Two horizontal dashed lines indicate the charge density limits for platinum and AIROF electrodes. This figure is published in colour at http://www.ingenta.com](image-url)
employed. The Shannon model relies on histological assessments of tissue damage from studies involving extended periods of pulsing (7 h) and it should be noted that the perceptual thresholds reported in Fig. 6 were obtained in acute studies using single pulses or short pulse trains and those perceptual thresholds that exceed the tissue damage boundary are unlikely to have caused tissue damage. However, damage thresholds for long-term chronic pulsing remain to be determined and it seems likely that more conservative limits than those defined in Fig. 6 will need to be adopted for long-term implants.

Although not directly comparable, some guidelines for safe stimulation may be taken from cochlear implant studies [102]. High current densities can produce histological evidence of nerve damage [103, 104], and some psychophysical studies have revealed increased perceptual thresholds when high current densities are used [104–106]. However, even intermediate current densities may produce transient elevations in thresholds, which suggest that mild dysfunction can be followed by tissue repair. These results are dependant on the type and geometry of the electrode, and on the species used in the animal model. It should also be noted that some cochlear implants have demonstrated a neuroprotective effect (increased survival of spiral ganglion neurons) in response to electrical stimulation that might lower thresholds [107]. This factor may mitigate some of the features discussed above.

One of the principle reasons that relatively large electrodes (>400 µm diameter) are employed for retinal prosthetic devices is concern that high charge densities will damage neighboring tissue or the electrode. However, to our knowledge, a firm relationship between charge/phase threshold and electrode size in target tissues for visual prostheses has not been established, perhaps because the amount of charge needed to damage the retina has not yet been determined. It is possible that thresholds decrease for smaller electrodes as the specificity of the stimulation applied increases. Examining this relationship is an ongoing area of research for the visual prosthesis community.

A LOOK TO THE FUTURE

Device resolution is presently restricted by many factors. Among the electronic concerns microelectronic design, packaging, electrode technology, power transmission and dissipation in tissue, and data telemetry rates figure prominently. From a biocompatibility perspective, charge density limits for electrode or tissue damage are a major contributor. If perceptual thresholds could be lowered, electrode size could be reduced without increasing charge density to unsafe levels. If this goal could be realized, it would make it possible to use a higher area-density of electrodes, which should theoretically improve the selectivity of neural stimulation and, presumably, the spatial detail of the induced visual images. A number of approaches to address the biocompatibility concern of decreasing charge thresholds for stimulation are being investigated. The strategy taken by most investigators is to decrease the spatial separation of the electrode and target population of neurons. In theory,
this approach should reduce stimulation thresholds, which might make stimulation safer and hopefully produce better visual outcomes.

Alternative electrode designs

Alternative electrode configurations may decrease electrode–tissue separation distances and thereby lower thresholds. For example, glass microwires have been used to create surface electrode arrays that can be curved to conform to the shape of the retina [108]. In preliminary experiments, activation thresholds of approximately 0.5–0.8 µC have been measured for retina, which is near the low end of reported results for surface stimulation electrodes (see Table 1). Unfortunately, this device employs electro-deposited nickel, which is known to be toxic to tissues, although the nickel could be protected with a layer of gold or platinum that would enhance biocompatibility.

However, an approach that will likely be more successful is the use of penetrating arrays. Studies of visual cortical stimulating electrodes consistently have shown that penetrating electrodes have lower charge thresholds than surface electrodes (Table 1). However, retinal and optic nerve prostheses presently use only a surface electrode design. In one conception of a penetrating array, networks of carbon nanotubes (CNT) have been used to penetrate the retina. CNT pillar arrays with a diameter of 50 µm and a height of 100 µm can perforate the retina without disruption of their mechanical integrity [109], and they have been shown to be “biocompatible” in retinal ganglion cell cultures, at least for 9 days [110]. However, electrical thresholds generated with such devices have not yet been determined. Although additional study is needed to further characterize these designs, penetrating electrodes that improve device-tissue proximity should certainly decrease thresholds and permit the use of smaller electrode sizes. The value created by penetrating electrodes in lowering activation thresholds is clearly evident from a comparison of the thresholds in Table 1 for surface and penetrating electrodes at the level of the visual cortex.

Another approach designed to decrease the separation distance between electrodes and target cells is in situ polymerization of electrically conducting polymers. Polypyrrole and polyethylenedioxythiophene (PEDOT) can be used as electrode materials for neural prostheses. Martin et al. [111–113] propose that these polymers can be injected into the target area and electrochemically polymerized from the electrode surface outward. Although there are substantial hurdles to clinical implementation (including potential aversion to in situ electro-deposition in the brain), this technique may allow electrodes to be grown directly in target tissue, improving separation distance.

Surface coatings

Another method for improving tissue-device contact is the use of surface coatings composed of patterned chemical cues. These coatings, which may include bio-
mimetic chemicals (i.e., mimicking native tissue with non-native molecules) or biomolecules, can reduce thresholds through two mechanisms. Surface modification can diminish immune response and, therefore, the formation of scar tissue. The diminished tissue responses will decrease the thickness and the electrical resistance of tissue lying between the electrodes and the target cells, which should substantially reduce thresholds and enhance implant performance. Alternatively, surface modification can promote neuronal attachment to the electrode surface, which should enhance the integration of the device with the host tissue and presumably lower thresholds. Unfortunately, bio-active molecules generally do not attract or promote adhesion of specific neurons. Undesirable glia (i.e., Müller cells, astrocytes) may be equally attracted, fouling the electrode surface and increasing the electrical resistance.

Studies using biomimetic surfaces are still in early phases, and potential improvements in threshold have not yet been demonstrated. However, alumina/zirconia ceramics have improved the biocompatibility of retinal implant packaging materials [114] and amorphous carbon deposited on sub-retinal implant materials virtually eliminated the fibrotic capsule [61]. Unfortunately, the exact mechanism for these beneficial responses is unknown. Coatings may either diminish the initial immune response or play a more active role in chronic implant tolerance. If it is the latter case, these results could be difficult to maintain, as creating coatings stable for the life of an implant may prove challenging. However, in pacemaker studies of biomimetic self-assembled monolayers (SAMs) of dodecanethiol, reduced acute inflammatory reactions promoted long-term improvement in pacing efficiency [115], suggesting that even acute changes in inflammatory response may diminish thresholds.

Biomimetic coatings have also been used to promote cell adhesion. For example, nanostructured porous silicon, which mimics microtubules found in the extracellular matrix, enhanced PC12 cell adhesion while reducing astrocytes adhesion [116]. Composite biomimetic-natural coatings, such as layer-by-layer films of polyethyleneimine and laminin, increased chick cortical neuron adhesion [117] while maintaining a low physical profile (approximately 3–11 nm). Thus, electrode–tissue separation distance resulting from the film itself was minimized. However, thresholds have not been measured for these systems.

The development of biomolecular coatings is more advanced. Surfaces coated with polylysine, laminin, or laminin peptides encouraged neuronal attachment to micropatterned substrates [118–122]. For visual prostheses in particular, laminin has produced neurite extension from PC12 cells and rat RGCs over patterns as small as 5 µm in width [123]. Subsequent migration of RGC axons toward the site of a stimulating electrode reduced thresholds by an order of magnitude [124]. This method supported neurite outgrowth from retinal explants for up to one month [122]. Nonetheless, as stated above, many biological coatings lack specificity in promoting cell adhesion, and the potential that a coating may encourage attachment of glial cells is a major concern [122, 125–127]
One limitation of these results is that threshold reductions were measured in vitro. The situation in vivo can be markedly different. In vivo conditions are very unlikely to provide direct contact of cells to tethered factors. Typically, target cells are embedded in several hundred micrometers of intervening tissue (e.g., approximately 100 µm [75]), and it is unlikely that tethered factors alone will successfully interact with cells across these distances.

**Tissue-engineered devices**

Tissue-engineering approaches, which attempt to reconstruct or mimic native tissue, may have more success in sustaining long-range interactions between target cells and the electrode surface. Several exploratory approaches for the merger of tissue engineering and implantable devices are being considered for use with a visual prosthesis. Electrode surfaces can be modified using techniques from tissue engineering to promote nerve growth to a target. For example, implanted cells cultured on micropatterned electrodes could extend neurites to the retina or brain [128]. Alternatively, physical or chemical cues may encourage growth of existing cells toward electrode surfaces [129, 130]. In either case, proposed devices would encourage cells to extend neurites over large distances. These extensions should produce more intimate contacts between electrodes and their targets, with the possibility of reducing thresholds, which have been quite high for patients with retinal degenerations (Table 1), who are the intended recipients for a visual prosthesis.

It has also been suggested that grafts of implanted cells and tissue could produce a synthetic “optic nerve” connecting a device to the lateral geniculate nucleus [128, 131–133]. This device, known as the hybrid retinal implant, would not require retinal ganglion cells or the optic nerve, and thus could treat a wide variety of ailments. The concept is exciting, but underscores one of the larger issues in tissue engineering today. Implantation of foreign cells and tissue will likely create an immune response in the host. While the immune system can be suppressed pharmacologically, it is unclear that the benefits of the device would outweigh the risks of immune suppression therapy. The hope is that suppression of interference by the immune system could be achieved locally, i.e., at the site of implantation or transplantation. For instance, membranes could be used to exclude immune elements [134], but the porosity required would likely be insufficient to permit regeneration of the implanted neurons to target tissue. Alternatively, allogeneic host cells and tissue, which would not evoke an immune response, could be cultured ex vivo and implanted with the device. However, it is improbable that adequate quantities of cells could be obtained, and function at the donor site would be lost. Technologies are currently not sufficiently advanced for a device using cellular implantation to find acceptance in the clinic. Although, as stem cell techniques advance, it may become possible to isolate cells from a patient for later implantation.

Other methods can circumvent these issues by utilizing physical and chemical cues to attract existing cells to the electrode surface. One device proposes to use
Retinal prostheses

Figure 7. Histological sections of the RCS rat retina 9 days after implantation. Retinal tissue (INL) migrates through the aperture of 40 µm in a 13-µm-thick Mylar membrane and spreads above the RPE. Scale bar is 50 µm. Figure reprinted with author and publisher (Institute of Physics) permission from Ref. [29]. This figure is published in colour at http://www.ingenta.com

the physical guidance of a micro-channel network to link cells with electrodes [135]. The premise is intriguing, as the researchers have already shown that retinal tissue will migrate through perforations in a Mylar membrane implanted sub-retinally (Fig. 7) [136–138]. It has also been suggested that electrodes coated with hydrogels partially comprised of extracellular matrix components (e.g., laminin, collagen) could release neurotrophic factors (e.g., NGF) that attract cells to the device surface [130]. In ongoing work in our laboratory, we have observed neurite extension in PC12 cells (Fig. 8) [129] and retinal explants (manuscript in review) in the presence of neurotrophin-eluting hydrogels. Neurites extended in response to released neurotrophins retract with neurotrophin removal; however, in the presence of cell adhesion molecules (i.e., laminin, collagen, or polylysine) extensions not only persist, but continue to grow.
Figure 8. Neurite extension from PC12 cells exposed to neurotrophin-eluting polymer hydrogels. After 9 days of culture, cells exposed to neurotrophin-eluting hydrogel boluses (A) display substantial neurite extension comparable to that of a positive control (B) receiving neurotrophin directly in solution. (C) Control cells receiving no neurotrophin display few, if any, neurites.

Either method will probably be successful in promoting nerve growth; however, several issues will need to be addressed in future research. Glia may also be attracted to electrode surfaces, which would likely diminish neuronal proximity to the electrodes and increase electrical resistance. It is unclear if neuronal function would remain unaltered after growth. Biochemical changes may modify neurotransmitter expression or cell firing. Further, regenerating neurons may create new synaptic connections, altering the visuotopic map in the retina or cortex.

SUMMARY

Great strides have been made in the visual prosthetic field over the two decades since its conception. Four companies are already performing long-term implants into blind human patients. The results of clinical testing are promising enough that continued work in the field is assured. However, many challenges remain for implementation in large patient populations. The electrical signal used will need to be non-damaging and contain the appropriate level of signal processing for the targeted cell type, and all of this must be accomplished using an adequate number of pixels for the desired acuity level. Pixel density is limited by high activation thresholds, resulting in part from the large separation distances between electrodes and target cells and the progression of degenerative diseases in target
patients. Stimulation values sufficient to achieve these thresholds may exceed electrode charge injection limits, and therefore require compensating increases in electrode area and concomitant decrease in pixel density and device resolution.

Comparisons to the cochlear prosthesis, which has had a very successful track record of restoring hearing to the deaf, provide hope and insight. The success of the cochlear prosthesis is particularly interesting in light of the fact that a relatively small number of electrodes (i.e., 6–18) are generally used. This suggests that plasticity of the cortex is able to accommodate the artificial electrical inputs to produce useful hearing. It is hoped that the brain will also contribute to the success of visual prosthetic devices. The success of a visual prosthesis may partly depend upon the ability to lower the relatively high stimulation thresholds that are found in patients with retinal degenerations, who are the primary intended recipients.

Emerging attempts to lower activation thresholds with bioengineering techniques are in the early development stage. These strategies primarily attempt to provide more intimate contact between the target cells and the device. Managing non-neuronal cell growth on these prostheses will be important to preserving the close proximity, and presumed threshold reduction, of the neural cells and electrodes. Polymeric coatings and drug-eluting polymers are likely to be involved in moderating both acute and chronic inflammatory responses to retinal prostheses and their development is being actively pursued. As these methods and materials advance, the potential for success for visual prosthetic devices will likely increase.

REFERENCES

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