Towards High-Resolution Optoelectronic Retinal Prosthesis

Daniel Palanker[a,b], Philip Huie[a,b], Alexander Vankov[b], Alon Asher[a], Steven Baccus[c]

[a] *Department of Ophthalmology, Stanford University, 300 Pasteur Dr., Stanford, CA 94305-5308;*
[b] *Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA, 94305-4085*
[c] *Department of Neurobiology, Stanford University, Stanford, CA, 94305*

ABSTRACT

It has been already demonstrated that electrical stimulation of retina can produce visual percepts in blind patients suffering from macular degeneration and retinitis pigmentosa. Current retinal implants provide very low resolution (just a few electrodes), while several thousand pixels are required for functional restoration of sight.

We present a design of the optoelectronic retinal prosthetic system that can activate a retinal stimulating array with pixel density up to 2,500 pix/mm^2 (geometrically corresponding to a visual acuity of 20/80), and allows for natural eye scanning rather than scanning with a head-mounted camera. The system operates similarly to "virtual reality" imaging devices used in military and medical applications. An image from a video camera is projected by a goggle-mounted infrared LED-LCD display onto the retina, activating an array of powered photodiodes in the retinal implant. Such a system provides a broad field of vision by allowing for natural eye scanning. The goggles are transparent to visible light, thus allowing for simultaneous utilization of remaining natural vision along with prosthetic stimulation. Optical control of the implant allows for simple adjustment of image processing algorithms and for learning.

A major prerequisite for high resolution stimulation is the proximity of neural cells to the stimulation sites. This can be achieved with sub-retinal implants constructed in a manner that directs migration of retinal cells to target areas. Two basic implant geometries are described: perforated membranes and protruding electrode arrays.

Possibility of the tactile neural stimulation is also examined.

Key words: Retinal prosthesis, neural cell stimulation, visual acuity

1. INTRODUCTION

As the population ages, age-related vision loss from retinal diseases is becoming a critical issue. Two retinal diseases are the current focus of retinal prosthetic work: retinitis pigmentosa (RP) and age-related macular degeneration (AMD). In these diseases, the "imaging" photoreceptor layer of the retina degenerates, yet the "processing circuitry" and "wiring" subsequent to photoreceptors are at least to some degree preserved. Retinitis pigmentosa occurs in about 1 out of 4000 live births, corresponding to 1.5 million people worldwide. This disease is the leading cause of inherited blindness. Age-related macular degeneration is the major cause of vision loss in people over 65 in the Western world. Each year 700,000 people are diagnosed with AMD, and 10% of these people become legally blind. Currently, there is no effective treatment for most patients with AMD and RP. However, if one could bypass the photoreceptors and directly stimulate the inner retina with visual signals, one might be able to restore some degree of sight.

One important factor affecting this strategy is that the absence of normal signaling from photoreceptors can lead to some progressive degeneration and mis-wiring of retinal circuitry [1, 2]. This type of degeneration is a general property of neural circuits. Thus, for an electronic implant to properly transmit visual signals to the inner retina, any degeneration of circuitry must not drastically change how these signals are interpreted by the higher brain. This is true in the case of cochlear implants, which bypass degenerated primary auditory sensory neurons; both the nerve and the downstream neural circuitry retain the ability to transmit interpretable auditory information.

Indeed, some first steps have been taken towards the development of an electronic retinal implant. It has been demonstrated that degenerated retina can respond to patterned electrical stimulation in a manner consistent with form vision[3-6]. Human patients implanted with an array of 16 (4x4) electrodes of 0.4mm in size can recognize reproducible visual percepts with patterned stimulation of the retina[3-6]. The patterns perceived by the patients did not always geometrically match the stimulation pattern, which is not surprising knowing the complexity of the retinal spatial organization. However, the one-to-one correspondence between the perceived and the stimulation patterns gives hope that with some learning and image processing the patients might be able to perceive useful visual information from this type of stimulation[7].

A large percentage of patients with age-related macular degeneration (AMD) preserve visual acuity in the range of 20/400 and retain good peripheral vision. Implantation would be worth its risk for such patients only if it

provided substantial improvement in visual acuity. In contrast, patients with advanced retinitis pigmentosa would benefit little unless there was enlargement of the central visual field enough to allow reasonable ambulation. Normal visual acuity (20/20) corresponds to an angular separation of lines by 1 min[8], which corresponds to spatial separation on the retina of about 10 μm, or in other words, spatial frequency F = 100 lines/mm on the retina. To provide such spatial frequency the stimulus pixels should have a linear pixel density at least twice higher: $P \geq 2F$, i.e. two pixels per line. In other words, to resolve two white lines at least one black line should be located in between. Thus the maximal spacing between pixels that will allow for resolving two lines separated by 10 μm is 5 μm. Similarly, spatial resolution corresponding to visual acuity of 20/400 corresponds to a pixel spacing of about 100 μm, while acuity of 20/80 (enough for reading with some visual aids) requires pixels smaller than 20 μm. For these estimates, it is understood that retinal stimulation by one electronic pixel may not produce a perceptual pixel-like "phosphene", and may generate more complex perceptions dependent on the precise number and connections of stimulated cells. What is essential in this analysis is the fact that pixel density determines maximal amount of information or maximal spatial resolution that can be provided by the stimulating array, and thus the best possible visual acuity, if the brain will be able to utilize all this information. Encoding of the information, i.e. conversion of the image from the video camera into the map of stimulating signals is a separate issue.

It has been previously estimated that 625 pixels can suffice for minimally resolving images in a tiny (1.7° or less) central field[9]. For functional restoration of sight a retinal implant should ideally cover a larger field of view – up to 10^o (3 mm in diameter), and support a visual acuity of at least 20/80 (corresponding to a pixel size of 20 μm and density of 2500 pix/mm^2) in the central 2-3^o of stimulating area.

Electrical stimulation of neural cells in the retina has been achieved with an array of electrodes positioned on either the inner[5, 9, 10] or outer side of the retina[11-13]. Setting the electrodes into the subretinal space so as to stimulate bipolar cells, although surgically challenging, has the potential advantage that signal processing in the retina is partially preserved. Full utilization of this advantage will probably require intervention at relatively early stages of retinal degeneration, before significant remodeling of the retinal neural network takes place[2]. Exciting the ganglion cells with electrodes positioned on the epiretinal side abandons the visual processing by the inner retinal network directly stimulating the output of the retinal circuitry.

One concern with either technique, pertaining to the goal of high resolution stimulation, is that the electrodes will always be some distance from the target cells. This occurs because the inner limiting membrane and nerve fiber layer intervene in the case of epiretinal approach, or because of photoreceptor remnants in the case of sub-retinal implantation. In addition, diseased retina may have an uneven thickness or wavy structure. Large distances between the cells and closely spaced electrodes result in cross-talk between neighboring electrodes, and the need for a high charge density and power for cell stimulation. This, in turn, can lead to erosion of electrodes and excessive heating of the tissue. Furthermore, any variability in the distance between electrodes and cells in different parts of the implant will result in variations of the stimulation threshold, making it necessary to adjust the signal intensity in each pixel. As we have shown earlier[14, 15] for chronic stimulation with pixel density of 400 pix/mm^2, which geometrically corresponds to visual acuity of 20/200, the electrodes need to be within 15-20 μm of the target neurons. For visual acuity of 20/80, the separation between electrodes and target cells should not exceed 7μm[14, 15]. Thus, ensuring a close proximity of cells to the electrodes is one of the most important unresolved issues in the design of a high resolution retinal prosthesis.

In this article we describe several techniques that may assure proximity of electrodes to the target cells. One of these techniques prompts migration of retinal cells into proximity of stimulating electrodes positioned in the sub-retinal space[16]. During migration the cells preserve axonal connections to the rest of the retina thus maintaining the signal transduction path. Another technique is based on an array of electrodes protruding from the sub-retinal chip[14].

A very significant problem with current designs of visual prosthetic systems is that they include head-mounted cameras linked (wirelessly) to the pixels on the patient's retina (Second Sight Inc.[6, 7], EPIRET Project[17], MIT-Harvard group[3]), so that eye movements are dissociated from vision. This dissociation compromises greatly the process of natural viewing. When the eye scans a scene, each movement is coupled to a strong expectation that the image will change accordingly. In addition, small eye movements during fixation are actually required for image perception: if an image is stabilized on the retina, it fades from perception within 100 ms [18]. Different approaches based on retinal chips that convert the natural image on the retina into electric signals (Optobionics Inc.[19], Retina Implant AG.[20]) do preserve the visual effects of eye movements. However, these systems are limited to (a) bright illumination conditions and (b) have no flexibility in image processing algorithms, which might be essential to compensate for lost image processing in the retina. In this article we describe the design of a system with a microcomputer-assisted interface and direct optical projection of the processed image onto photosensitive pixels in the

retinal implant using near-infrared light. This system should allow for natural eye scanning and enable the simultaneous use of implant-stimulated vision and any remaining normal vision at any level of luminance.

Another important aspect of macular chip design is adjustable image processing. Synaptic connections from foveal photoreceptors radiate out to bipolar and ganglion cells at some distance from the visual center. Thus, an image centered on the foveola will be processed by bipolar and ganglion cells in a circular zone outside foveola. Prosthetic chips will need to have stimulus signals that match this neural anatomy. The system described below includes location-dependent image processing based on a precise tracking system that monitors the location of the implant in real time. Stimulation of neurons by the retinal implant differs from natural retinal signal processing. Therefore, to enable the translation of stimulus patterns into the conscious recognition of objects, visual chips may require some form of image processing and neural "learning", much as is required by modern cochlear implants. Tracking the implant in real time allows for the position-dependent image processing that may be required to translate visual information into electrical signals that can be properly interpreted by the higher brain.

In the article below we describe a system that addresses all three issues raised above: (a) proximity of electrodes to the target cells, (b) delivery of information associated with the natural eye movements, and (c) location-dependent image processing.

2. ATTRACTING RETINAL CELLS TO ELECTRODES

2.1 Migration of Retinal Cells into Perforated Membrane

Recently we have discovered a robust and unexpected property of retinal tissue that promises to reliably and chronically maintain the retina in extremely close proximity to the implant, allowing high-resolution electrical stimulation. In experiments *in-vitro*, in which retinas were placed photoreceptor-side down upon the membrane, a robust migration of retinal tissue into small apertures was observed in all samples of the rat, chicken and rabbit retina[16]. Migration of the outer nuclear layer, outer plexiform layer and inner nuclear layer occurred through apertures larger than 5 μm. The cellular invasion of the aperture appeared to include both glial and neural cellular elements, and the rate of tissue migration increased with aperture size. A transmission electron micrograph of a section through an aperture demonstrated the presence of neuronal processes and synaptic structures connecting the migrating cells. These finding indicate the possibility of signal transduction from the stimulated cells to rest of the retina.

Culturing of the retina upside down (tested on the P7 rat retina), i.e. nerve fiber layer towards the membrane, did not result in cellular migration.

The RCS rat was used as a model for *in vivo* experiments, since the photoreceptors degenerate as in RP. Experiments with subretinal Mylar films perforated with apertures of 15 - 40 μm in diameter showed robust migration of the inner nuclear layer after 5 and 9 days [16]. Since unlimited tissue migration through a membrane could be problematic (draining retinal cells and proliferating under the prosthesis) we explored the placement of perforated membranes with a basal seal to prevent growth out the bottom. These experiments were performed in-vitro with cultured rat retinas. As shown in Figure 1, the 20 μm perforations lay atop a small chamber, and the bottom was sealed with a membrane. When retinas were cultured over this 3-layer structure for 7-14 days, tissue was observed to migrate into the chambers but no further (Figure 1B).

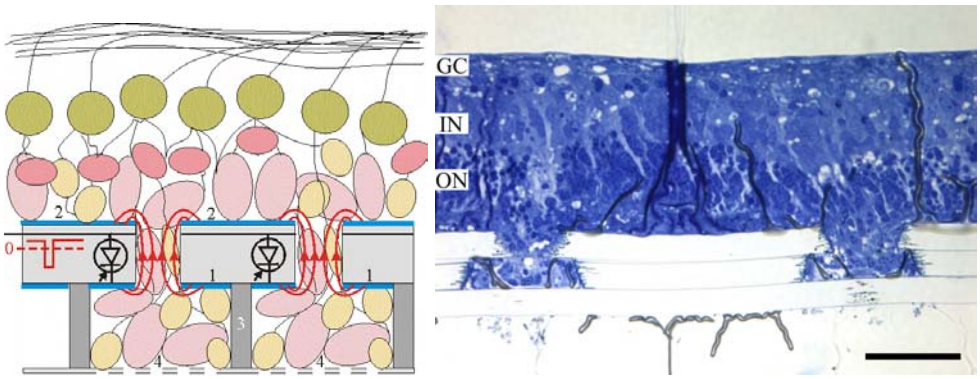

Figure 1. A. Schematic of a 3-layered membrane with entry channels on top, wider inner chambers, and a fenestrated membrane (4) at the bottom. Voltage can be applied between the inner electrode (1) and the common return electrode (2). **B**. Rat retina grown on the 3-layered structure for 7 days in-vitro. Retinal cells migrated through the 20 and 35 μm holes into the middle chambers of 60 μm in width, but not through the 3 μm holes in the lower membrane. Scale bar is 50 μm.

Major concerns are whether the neural cells that migrate into the pores will survive for an extended period of time, whether the neural circuitry will be disrupted and whether the migrated tissue will change through glial

overgrowth or cell death. The long-term behavior of retinal cells migrating into perforated membranes should be further studied to optimize the membrane structure for preserving neural connections and assuring efficacy of an electric interface.

2.2. Migration Around Protruding Electrodes

Another promising technique for providing close proximity between the neural cells inside the retina and the stimulating sites of the implant involves protruding electrodes. As diagrammatically shown in Figure 2A, stimulating electrodes (1) would extend by several tens of micrometers above the surface of photodiodes and be exposed only at the top of the "pillars", with a common return electrode (2) on the surface of the wafer. This array would be positioned in the sub-retinal space, so that cells could migrate into the empty space between the pillars, similarly to the migration we observed with the perforated membrane. This way the electrodes will penetrate into retina without mechanical stress and associated injury. This technique is complimentary to the perforated membrane in a sense that the cells which do not migrate and thus remain in the depth of retina can be stimulated by the penetrating electrode, as opposed to the perforated membrane; where only the migrating cells that will penetrate into the bottleneck of the chamber can be stimulated. The depth of penetration will be determined by the length of the pillars. The pillars can be manufactured using conventional photolithographic technology.

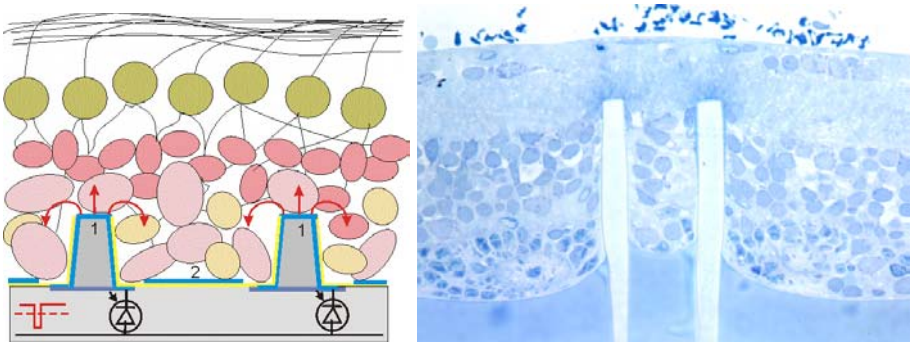

Figure 2 A. Concept of protruding electrodes on the sub-retinal array penetrating deep into the retina after migration of the retinal cells in between the pillars. Pillars are insulated at the sides and exposed at the top, penetration depth is set by their length. **B**. Lithographically-fabricated 10 μm-wide pillars penetrating into the inner plexiform layer in the retina of RCS rat 15 days after implantation.

To demonstrate the feasibility of this design, we manufactured an array of pillars of 70 μm in height and 10 μm in diameter using photolithography with SU-8 photoresist. We implanted these arrays into the subretinal space in adult rats with retinal degeneration. Histology performed on eyes enucleated 15 days after the implantation is shown in Figure 2B. As one can see in this Figure the retina is well preserved with the inner nuclear layer slightly disturbed by the pillars that penetrated into the inner plexiform layer. Shorter pillars will be used for addressing the inner nuclear layer.

3. DELIVERY OF INFORMATION AND POWER TO THE IMPLANT

3.1. Projection system

The projection system is designed to allow natural eye scanning for image perception, flexibility of image processing between the camera and the implant, and utilize any remaining intact vision. The system controls the stimulating signal in each pixel by projecting light from the goggles display onto a retinal implant with an array of powered photodiodes, as diagrammatically shown in Figure 3. An image from the small video camera located on the patient's goggles is processed using a portable microcomputer (pocket PC). The processed image is displayed on the LCD micro-display similar to those used for "virtual reality" imaging systems (medical, military, etc.). The LCD display will emit near-infrared (IR) light (800-900 nm). The IR image from the display is reflected from the transparent goggles and projected onto the retina using natural optical properties of the eye, as shown in Figure 3. The projected IR image is thus superimposed onto a normal image of the world observed through the transparent goggles. The retinal chip has an array of photo-sensitive elements converting the IR light into stimulating current in each pixel using a pulsed bi-phasic power provided by a photovoltaic battery, or otherwise, as described below. Advantages of this system as compared to current approaches to visual prosthesis include:

- Transmission of information from the LCD screen to each pixel in the chip is conducted by light simultaneously, i.e. pixels are activated in a parallel fashion, and there is no need for serial decoding in the implant, as it is done for the single emitter-receiver links (either optical[17] or radio frequency[3]).

- The IR video display on the goggles can emit as much power as the eye can thermally tolerate thus providing a robust signal to each pixel at any level of ambient illumination.
- The system's design allows implant-stimulated vision at the same time that residual natural vision of the patient functions normally in the areas outside the retinal implant. The infrared projected image is not detected by normal vision. Conversely, the implant's infrared sensitivity is such that its response to visible light is negligible compared to the bright infrared image. The tracking system that monitors the position of the implant at each moment (described below) will allow for alignment of the stimulated parts of the image and those perceived normally.
- The video display projects an image corresponding to the field of view which is much larger than the retinal chip (typically covering only a small solid angle). With this system, the patient can use his natural eye movements in order to observe the larger field of view, rather than scanning the field of view by moving his head-mounted video cameras.
- Intensity, duration and repetition rate of the stimulating signal produced by the retinal chip can be controlled by the intensity, duration and repetition rate of the light-emitting pixels in the screen. These parameters can be adjusted without need for any changes in the retinal chip itself. This feature provides flexibility in optimization of the stimulation parameters and image processing algorithm, which might have to be adjusted for each patient.
- This projection system can be used for both epiretinal and subretinal implants.

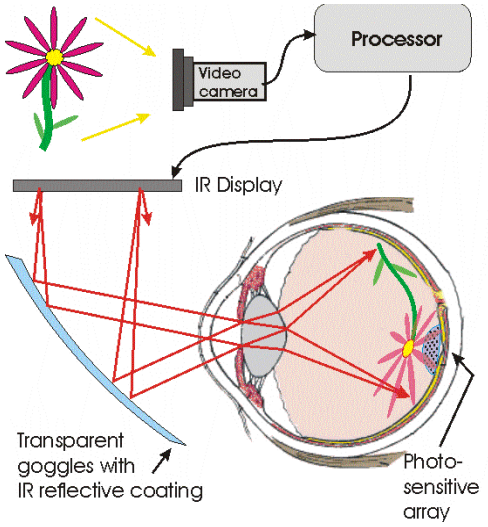

Figure 3. Image projection from the goggles display onto retina. Part of the image which is projected onto retinal chip activates its photo-sensitive stimulating pixels.

As described above, the stimulation current for an electrode of 10 μm in diameter is on the order of 1 μA. The photodiode converts photons into electric current with efficiency of up to 0.6 A/W, thus 1.7μW of light power will be required for activation of one pixel. If light pulses are applied for 1 ms at 50Hz, the average power will be reduced to 83 nW/pixel. With 18,000 pixels on the chip, the total light power irradiating an implant will be 1.5 mW.

LCD screens used in video goggles emit light into a wide angle, and only a small fraction of it (typically <1%) reaches the retina, while most of it is absorbed by the sclera and iris. In addition, only a small part of the retina (about 5%) is covered by an implant which requires high brightness, while peripheral vision can operate at natural (much lower) level of luminance. To provide 2 mW of light on a 3 mm retinal implant, the LCD goggles should in total emit about 4 W of light power! This is certainly not practical.

This problem can be resolved by addressing both aspects of the loss of light: (1) providing a collimated illumination and (2) activating at high brightness only a small part of the screen - that which is projected onto the implant, position of which will be constantly monitored with a tracking system (Figure 12). The high brightness pulsed illumination for the implant will be provided by the near-IR LED array positioned behind the LCD screen, as shown in Figure 4. A condenser lens directs the main axis of the diodes into the center of the eyeball. Assuming no magnification between the screen and the retina, the diameter of the light spot on the pupil will be $D = d_{chip} + \alpha L$, where d_{chip} is the implant size, $\alpha = 8^{o}$ is the divergence of the LED beam, and L=17 mm is the distance between the implant and the pupil. With these assumptions the spot of light on iris will be 5.3mm in diameter. With the pupil of 3mm in diameter, 32% of light will be transmitted into the eye, thus only 6 mW of power in the region covering the implant would be required from the LCD screen.

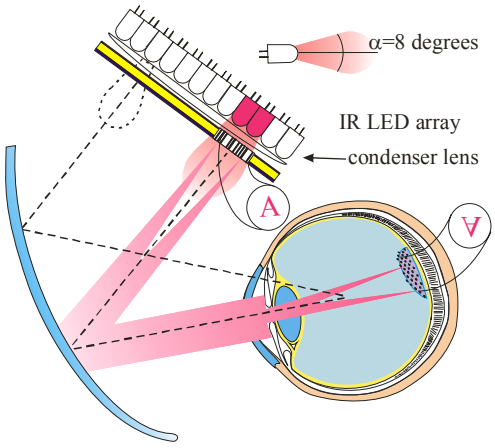

Figure 4. Diagram of the LED array for collimated illumination of the LCD screen.

3.2. Location-dependent image processing

The central part of the macula (fovea) does not contain bipolar and ganglion cells. Photoreceptors in this area radiate their synaptic connections outside the fovea (Henle's fibers), to a distance of about 0.5mm in diameter, as shown

in Figure 5. Thus if the retinal chip covers the macula, the image should be processed so that stimuli are delivered to the bipolar or ganglion cells outside the foveola. This means that an image projected onto the retinal stimulating array should have a black spot in the foveola (since there are no cells to stimulate in that area), and the rest of the macular area should be stretched in a radial pattern matching the retinal organization in the macula, as shown in Figure 5. An example of such image processing is shown in Figure 6. The fact that retinal architecture is non-uniform around the center of the macula necessitates image processing that depends on position of the foveola relative to the projected image, i.e. it depends on direction of gaze.

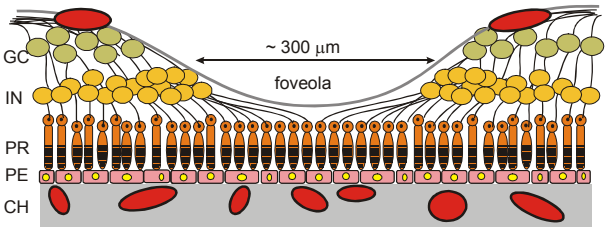

Figure 5. Diagrammatic representation of the human fovea with bipolar and ganglion cells located outside the foveola. Labels of the retinal layers: GC- Ganglion cells, IN – inner nuclear, PR – photoreceptors, PE – retinal pigmented epithelium, CH – choroids. Red ovals inside the choroid and above the GC layer are blood capillaries.

There are several additional reasons necessitating the position-sensitive image processing for the visual chip controlled by the optical projection system:

- The retina has a complex system of image processing involving intertwined patterns of "ON" and "OFF" cells with large receptive fields having center-surround organization. For correct transmission of the image there might be a need for the stimulation pattern matching this cellular organization. In addition, there might be a need for temporal variation of the stimulation of the neighboring pixels[21].

- Part of the retinal implant system might be a photovoltaic cell that generates power for the stimulating array. To generate power at maximal efficiency, the region of the display imaged onto the battery could emit continuous bright light (Figure 6).

- Various pixels in the array may have different impedances (due to the tissue growth or electrode contamination) or different distances from the cells and thus may require different pulse characteristics such as intensity or frequency.

Because the image processing between the video camera and the IR LED-LCD array that transfers information to the implant should depend on the position of the implant, a real-time tracking system is required.

Figure 6. Left: A wide view of a scene by the video camera. **Right:** The same image processed for the position of the macula centered on the right edge of the traffic light. Black spot corresponds to foveola, where no cells will be stimulated. Pixels around the black spot are stretched radially in order to match retinal architecture (lighter circle). A white circle indicates a part of the display projected onto a photovoltaic battery located on retina aside the stimulating chip. The rest of the image represents a view through the transparent goggles for the remaining natural vision of the patient.

3.3. Implant tracking system

Since the eye is frequently moving, fixating on different parts of the image, the proper image processing and activation of the display requires information about the position of the retinal chip at each moment. Therefore, another aspect of the projection system includes a tracking system (Figure 7) for the optically-activated retinal chip. This system monitors positions of a few reference points on the retinal implant. The reference points reflect or emit light back through the pupil and are imaged onto the tracking array which is positioned in the conjugated plane with the LCD display. For tracking the location and torsional orientation of the retinal chip only 2 reference points on its surface should be sufficient. More reference points may provide higher reliability and precision in localization of the chip. During fixation, the human eye drifts at an average angular velocity of 0.5 deg/s, up to 2deg/s [22]. In contrast, during saccades, large ballistic movements, the eye can move with a velocity of hundreds of degrees per second. However, normal visual perceptionis greatly decreased during saccades, especially to motion, so real-time image processing will not be required at these rates.

Reference points on the implant can be made, for example, in the shape of 3-sided pyramidal indentations with highly reflective walls, thus reflecting light in the direction of incidence. They also may be made as small LEDs

emitting a wavelength or temporal pattern different from that emitted by the image display. This will allow for discrimination between the emission by the reference points and scattering from elsewhere in the eye. To allow for localization of the reference points with a spatial resolution of a half of a pixel in the implant (10 μm) the tracking system should have angular resolution of 0.03 degree. Thus, the imaging array of the tracking system, having a visual field of 30 degrees should have at least 1000 pixels in a row. Modern video cameras have 1600x1200 pixels with a frame rate of 30 Hz, providing a dynamic range of 8 bits (gray scale), which is well suited for this application.

Knowing the current position of the chip and relation of the fovea to the chip, the image on the display will be adjusted appropriately. For example, the pixels in the center of the field of view can be distributed peripherally a few hundred microns to accommodate the absence of foveal circuitry, the power supply (photovoltaic cell) will be properly illuminated, and the relative intensities and delays in different pixels will correspond to the required pattern on the chip. Software for this type of real-time image processing is currently under development and testing in our group.

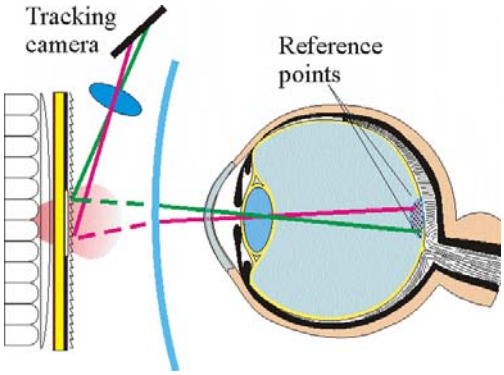

Figure 7. Tracking system monitoring position of a few reference points on the retinal implant. View from above. LCD and tracking camera are above the eye level.

3.4. Optoelectronic implant design

As described above, proximity of retinal cells in the inner nuclear layer to the stimulating electrodes can be achieved by promoting cellular migration into the sub-retinal implant. One possible design of a sub-retinal photosensitive stimulating array that takes advantage of this effect is shown in Figure 1A. A wafer of about 15-25 μm in thickness is divided into separate photosensitive pixels similarly to a CCD array. In each pixel, there is a channel of about 5 – 15 μm in diameter for cellular migration. Each pixel is a biased photodiode which converts light intensity into biphasic charge-balanced pulses. All the pixels are connected to one common biphasic power line. The negative phase of the waveform is transmitted through the photodiodes as a function of light intensity. The positive phase passes through the diodes providing compensation for the charge balance. To avoid irreversible electrochemical reactions on IrOx electrodes, the voltage is limited within the range -0.6 +0.8 V, and charge density is limited to 4mC/cm^2 [23, 24]. In preliminary experiments with such circuits we verified preservation of the charge balance with precision better than 0.01% independently on the light intensity in individual pixels. The stimulating bi-phasic pulse conducted through the photodiodes is applied to the inner electrode (1) in the cavity, while the return electrode (2) is transparent and common to all pixels in the array. To form a cavity the wafer is mounted on a spacer layer (3) which is closed on its lower side with a perforated membrane (4) limiting cellular migration but allowing for a flow of nutrients and oxygen. An electric field is applied between the electrodes 1 and 2, stimulating the cells located at the "bottleneck" of the channel, as shown by red arrows in Figure 1A. Alternatively, the addressable electrodes are positioned at the bottom of each chamber, while the upper membrane is a simple perforated insulator with a conductive coating at the top. The semiconductor wafer at the bottom in this case has no perforations and thus its manufacturing is conventional and inexpensive. The current from the lower electrode in each chamber is concentrated inside the aperture in the upper membrane and thus the cells located in and near this bottleneck will be affected by electric field the most. In case the cells inside the chamber do not survive for extended periods of time, cells in the bottleneck will still be stimulated. Furthermore, even if cells in the bottleneck are not functional, the stimulation zone can be extended up and around the aperture by positioning the return electrode slightly away from the edge of the aperture.

An upper estimate of the current, charge density and power dissipation can be given assuming that the cells located in the bottleneck do not increase the electric impedance between electrodes 1 and 2. Impedance of the 15μm-long channel of 10 μm in diameter filled with physiological medium is about 150 kOhm. The charge transfer resistance and the resistance of the oxide layer for IrOx electrode of 10 μm in radius will add another 50 kOhm. An electric field of 30 V/cm (threshold for cellular stimulation) corresponds to a current density of 0.4 A/cm^2, thus resulting in the total current of about 0.3 μA across this channel. If the maximal signal is 10 times above the threshold value (i.e. 3 μA), the total charge transfer during 0.5 ms pulse will be 1.5 nC. For the inner electrode of 10 μm in radius, the charge density will be about 0.5 mC/cm^2, which is well below the safe limit of 4 mC/cm^2 for an IrOx electrode [23, 24]. Pseudocapacitive voltage steps at the electrode-liquid interface will reach 100 mV by the end of each pulse. The heat

generated during a 1 ms pulse (two phases of 0.5 ms each) is about 3 nJ. If applied at repetition rate of 50 Hz the average heating power will be 150 nW. Even with 18,000 pixels the average power will not exceed 2.7 mW.

Photodiode conversion efficiency (light-to-current) is typically less than 0.6 A/W, thus for generation of 3 μA of current about 5 μW of light power will be required in each pixel. For a pixel size of 20 μm this amount of power corresponds to an irradiance of 13 mW/mm^2. If pulses of 0.5 ms in duration are applied at 50 Hz the average power density will be 0.31 mW/mm^2. For a chip 3 mm in diameter the total average power will thus be 2.2 mW. Together with electrical power estimated above, the total power dissipation at maximal stimulation level (10 times the threshold) on all 18,000 pixels in the implant will be about 5 mW. This corresponds to the temperature rise of 0.7 ^{o}C at the surface of the 3 mm disk array. This level of chronic heating at maximal stimulation level seems acceptable. If heating becomes a problem, the repetition rate could be reduced to 25 Hz or even 15 Hz, thus producing "slower" vision, as occurs in human perception in near darkness. As described above, only the image projected onto the retinal chip will be illuminated brightly with IR light. The rest of retina will receive natural image through transparent goggles.

If, in fact, the bottleneck of a chamber is partially blocked by a cell, increasing the impedance in parallel to the cell, this is actually an advantage because the required voltage drop across the cell will be achieved at a lower current. However, encapsulation of electrodes surfaces with glial layer might be a problem, since this might disconnect the electrodes from the medium, increasing the impedance in series with the cell, requiring a greater voltage to stimulate the cell. Encapsulation might be prevented using coatings that can inhibit glial cell growth and fibrosis[25].

An alternative approach to placing the electrodes in close proximity to the cells using penetrating electrodes is shown in Figure 2A. The biased photodiodes will have lithographically-made pillars with a conductive coating extending several tens of micrometers above the wafer. The pillars will be insulated except for the top, where an electrode (1) coated with IrOx will be exposed. The common return electrode made of a transparent conductive material will cover the rest of the surface of the array (2). The implant positioned into the sub-retinal space induces migration of retinal cells into the spaces between the pillars, thus allowing for pillars to penetrate to the depth determined by their length, as shown in Figure 2B, without forceful insertion and associated mechanical injury.

In this approach the actively migrating cells will move towards the bottom of the implant while allowing the electrodes to reach the cells which migrate slower or do not migrate at all. The pores and pillars approaches are complimentary: in the first case the actively migrating cells penetrate into the pores and are stimulated. In the second case the migrating cells move towards the bottom of the implant and the electrodes approach the cells which remain in place.

3.5. Power Supply

As described above, the optoelectronic prosthesis having 18,000 pixels and 10 μm electrodes can consume up to 3 mW of power from the bi-phasic power supply. This power can be generated inside the eye with photovoltaic batteries using part of the light projected from the goggles. The most efficient place for collection of the ambient light is the anterior chamber, for example, in front of the iris, as shown in Figure 8. The power supply will consist of two segments generating voltages of opposite polarity, and a switching mechanism that will apply bi-phasic pulses to the retinal stimulating array. The implant is a thin (25 μm) wafer with photovoltaic cells and pulse generator encapsulated in a transparent biocompatible coating. As we estimated above, with a pupil of 3 mm in diameter 3 times more power falls on the iris than on the retinal implant, thus providing adequate amount of light for the anterior photovoltaic battery.

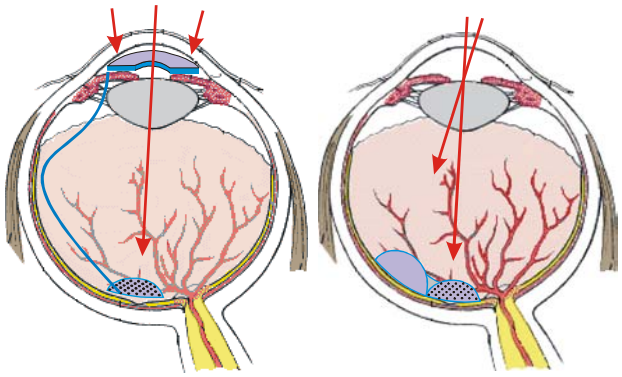

Figure 8. The retinal implant converts an image into the stimulating signal using the energy of the photovoltaic power supply located in the anterior chamber (left) or next to the stimulation array (right).

Placement of the photovoltaic battery in the anterior chamber, although beneficial from the optical point of view, is surgically challenging since it requires connecting the two independently placed implants (retinal and anterior) with a wire. Alternatively, the photovoltaic battery can be placed on the same implant with the stimulating array, which makes the surgical procedure significantly simpler. In this case the LED-LCD screen should emit an additional pattern of light projected onto the photovoltaic battery, as shown in Figure 6. Since not more than 30% of light energy can be converted into electrical energy, not less than 9 mW of light power should illuminate the battery in order to generate the required 3 mW of electric power. To avoid heating the retina by more than 1 ^{o}C, the total power dissipation by the

power supply should not exceed 7mW, and thus the repetition rate of stimulation in the implant might need to be reduced from 50 to 25 Hz. Alternatively, a power supply can be based on RF transmission of energy from the coil located on the goggles into a coil inside or outside an eye.

4. TACTILE STIMULATION USING OPTO-MECHANICAL ARRAY

Electric depolarization of the cell membrane is not the only mechanism of neural cell stimulation. Tactile sensitivity is based on response of the ion channels to mechanical deformation of the cellular membrane. All neural cells are sensitive to deformations, while some are more specialized than others. For example, tactile sensors in skin are sensitive to deformations of about 0.3 μm in amplitude. It has been demonstrated that tactile sensors can create synaptic connections in-vitro with cells they are normally connected in the organism[26]. In the preliminary experiments we observed stimulation (with fluo-4 imaging) of the RGCs by slight deformations induced with a micromanipulated probe.

Tactile sensitivity of neural cells might be used for retinal generation. These cells could be either autologous tactile cells, for example from skin, or the retinal neural cells attracted to the chip. This approach could have many advantages for the retinal prosthesis: (1) Stimulation of the neurons by mechanical deformation is natural to tactile-sensitive cells, as opposed to electrical excitation. (2) This technique has no electrochemical toxicity and no heat-related concerns. (3) It allows for very high resolution since the pixels are of a cellular size, and the mechanical cross-talk between neighboring pixels is very low.

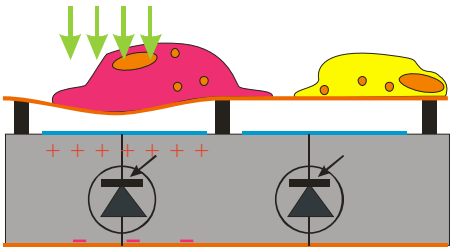

Figure 9. Neural cells grown on electro-statically deflectable membrane can be mechanically stimulated by illumination of the photodiodes. Electric charge transmitted through the illuminated photodiode induce an opposite charge on conductive membrane, attract and deflect it.

A photo-deflectable chip design is shown in Figure 9. It consists of a thin conductive and transparent flexible upper membrane separated from an array of photodiodes by the micrometer-high spacers. The membrane and the photodiodes underneath are divided into pixels of a cellular size (10-20 μm in width). The photodiodes are connected to a common power line on the lower side of the implant. Upon illumination, the photodiode becomes conductive to electric current and an electrode under the deflectable membrane becomes charged. This charge induces an opposite charge on the membrane, and the attraction of these charges deflects the membrane towards the photodiode. A cell grown on the membrane deforms and thus, due to its tactile sensitivity, stimulated. The amplitude of the deflection is determined by the amount of charge transmitted through the photodiode, which is determined by the local light intensity. This mechanism of cellular activation can also be applied in a pulsed regime, when the photodiodes are powered by the pulsed voltage, and the amplitude of oscillation in each pixel is determined by the local luminance. Alternatively, constant voltage and pulsed illumination could be used.

With a pixel size of 10 μm, a silicon-based membrane of 0.15 μm in thickness will deflect by 1 μm at the applied voltage of 10 V. Capacity of the air-gap capacitor of 10 μm in width and 1 μm spacing between the electrodes is 1 fF. The energy stored in such capacitor at 10 V is 50 fJ. With a repetition rate of 50 Hz the power consumption will be 2.5pW per pixel. An implant on 3 mm in diameter will contain 700,000 such pixels and will consume only 1.8 μW of power. This pixel density geometrically corresponds to visual acuity of 20/40!

To apply this technique to retinal stimulation two approaches can be undertaken: (A) growing the autologous tactile sensory cells extracted from skin on the deflectable membrane, and forming the axonal connections between them and the neural retinal cells in the inner nuclear layer. (B) Attracting the cells from the inner nuclear layer to the chip and stimulating them utilizing the sensitivity of all neural cells to mechanical deformation of the cellular membrane (Figure 10).

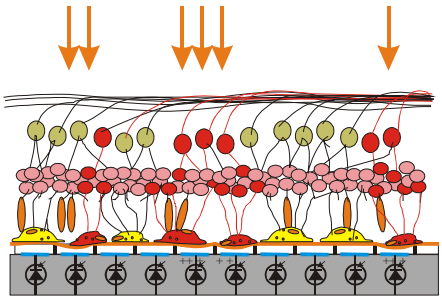

Figure 10. Photo-deflectable membrane chip with tactile sensors positioned in the sub-retinal space. The tactile-sensitive cells are stimulated by mechanical deformations and transmit the signal to the inner nuclear layer.

5. ADVANCED SIGNAL PROCESSING

Since stimulation of neural cells by the retinal implant differs from the natural mechanisms of visual signal processing in the retina, restoring natural sight will require the combination of a number of factors. Perhaps the most important will be plasticity of neural networks that will learn to interpret electrical stimulation of the partially degenerated retina. To minimize the reliance on neural plasticity, it is desirable for the stimulated signals to match as closely as possible natural visual responses. This is most likely if the implant is placed as early in the visual system as possible. In addition, placing the implant early in the visual pathway takes advantage of existing downstream neural processing, and minimizes the necessity of electronically preprocessing the image so as to reproduce the processing of bypassed neural circuitry. In cases of complete photoreceptor degeneration, the earliest point an implant can stimulate is bipolar cell dendrites. Thus, two main aspects of visual processing that would likely be compromised are color processing, which arises by virtue of different cone types, and separation of neural signals into the ON and OFF pathways, which occurs at the photoreceptor-bipolar synapse. Though the absence of color vision would prevent some object discrimination, it would still allow the detection of the presence of objects. As to the ON and OFF pathways, an implant that depolarizes neurons in response to an increase in light intensity would stimulate the ON pathway with the correct sign, but the OFF pathway would receive an inverted signal. However, many visual neurons have rectified responses, responding to either sign, and thus a number of aspects of visual processing might not be substantially affected. For example, many ganglion cells are of the "ON-OFF" type, responding to either increases or decreases in light intensity. Additionally, in the retinal pathway that distinguishes moving objects from background motion, signals are rectified, and exchanging black for white does not change the firing patterns of object motion sensitive retinal ganglion cells[27].

Advanced processing of the image could potentially restore an even higher level of vision, though these methods would be most affected by the precise level of degeneration of retinal circuitry. Both correct color and contrast processing could conceivably be restored if the visual scene was preprocessed in different ways appropriate to the separate pathways and then addressed separately to those pathways. This becomes possible with a precise tracking system that can detect the location of the implant in real time. In addition, it would require that individual electrodes only communicate with a single channel of contrast (e.g. only ON or only OFF cells). Electrodes of 10 μm in size might enable this level of selectivity. Which cell types are, in fact, activated by individual electrodes will be determined in animals by application of various stimulation patterns while recording from ganglion cells with a multielectrode array[28, 29]. In humans this function would be performed based on communication with the patient.

In summary, (a) high enough resolution for useful vision cannot be achieved unless very close proximity (on the order of cellular size) between the electrodes and target cells will be established along the whole interface of the implant with the retina. (b) For normal visual perception the image should not be dissociated from the eye movements and (c) the image processing between the camera and the implant should depend on the implant location, i.e. direction of gaze. The system described in this article includes (1) an optically controlled implant enabling delivery of visual information related to the natural eye movements, (2) position-sensitive image processing, and (3) techniques for bringing retinal neurons into required proximity with stimulus elements.

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