Artificial Vision Project by Micro-Bio Technologies

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Abstract

A number of research groups worldwide are studying electronic implants that can be mounted on retina/ optic nerve/ visual cortex to restore vision of patients suffering from retinal degeneration. The implants consist of a neural interface made of biocompatible materials, one or more integrated circuits for stimuli generation, a camera, an image processor, and a telemetric channel. The realization of these classes of neural prosthetic devices is largely due to the explosive development of micro- and nano-electronics technologies in the late 20th century and biotechnologies more recently. Animal experiments showed promise and some human experiments are in progress to indicate that recognition of images can be obtained and improved over time. We, at NBS-ERC of SNU, have started our own retinal implant project in 2000. We have selected polyimide as the biomaterial for an epi-retinal stimulator. In-vitro and in-vivo biocompatibility studies have been performed on the electrode arrays. We have obtained good affinity to retinal pigment epithelial cells and no harmful effect. The implant also showed very good stability and safety in rabbit eye for 12 weeks. We have also demonstrated that through proper stimulation of inner retina, meaning vision can be obtained.

Keyword : retinal degeneration , neural interface , retinal implant , electrode arrays

1. Introduction

Vision is enormously complex form of information processing that depends on a remarkable neuroprocessor at the back of the eye called the retina. Roughly 130 million photoreceptor cells in the retinal layer can get light signals into neuronal signals to the next stage. But, Retina cannot compensate well for damage or deterioration. In particular, vulnerable light sensitive rod and cone receptors located at the back of the retina can suffer from Aging macular degeneration (AMD), Retinitis Pigmentosa(RP) and laser injury in war or work. In the case of AMD, the probability that people suffer from this disease is 0.025 percent of normal (1 over 4000 people). RP is more serious that probability is 5 percent of normal (1 over 20 people). According to the handicapped level table of Korean reparation enforcement ordinance, total blind is acknowledged as 100% loss of their labor power. Though one side of eyes is blind, it is treated as 60% lost of labor power.

Thus losing sight is a threat to the welfare of human-being. To solve this fatal problem, artificial vision came up to the surface as an alternative. Artificial vision starts at the neuronal action potential can be evoked by external current stimulation. This basic concept variably directs Artificial-vision strategies [1, 2].

One of strategies is cortical implant. At 1970's, Dobelle group implanted cortical stimulator on 41 patients. Just two of them are still put it on for over 20 years. One of Two patients can recognize the black hat hanged up at the white wall [3, 4]. Another strategy is optic nerve implant. Optical path is consists of several stages. Optic nerve is the second stage that almost 1.2milion numbers of nerve fiber are summed up and forms one strand. In 1998, Belgium group implanted the cuff shape electrode arrays surrounding optic nerve on human [5]. The work is still in process with some remarkable results.

In the case of retinal implant, there are two kinds of approach. One is Epi-retinal implant, the other is sub-retinal implant. Retinal implant starts from the papers those clarify the result, electrical stimulation on the ganglion cells those were in the retina lost its function can be stimulated and occur phosphenes [6, 7]. Epi retinal implant approach stimulates retinal ganglion cell that extends to the optic nerve. At present MIT & Harvard and Johns Hopkins University (JHU) in USA take active part in this type of research [8-10]. It is implanted on the retinal surface with some fixing devices like micro retinal tack [11] or medical glue. Sub-retinal implant approach replaces only photo-receptors, and uses the

rest of retinal function effectively. It is implanted between retina and sclera layers, and doesn't need any fixing devices. Interlayer fixing can effectively maintain the electrode at the targeted position. University of Illinois in USA and Tuebingen University in Germany are active groups in this strategy [12-14].

2. Recent status of groups

2.1 Cortical Implant

A patient was implanted with 68 electrodes on the visual cortex and reportedly could read the 2-inch tall letter at a 5 meter distance [4]. After this report, however, no other advances were reported elsewhere.

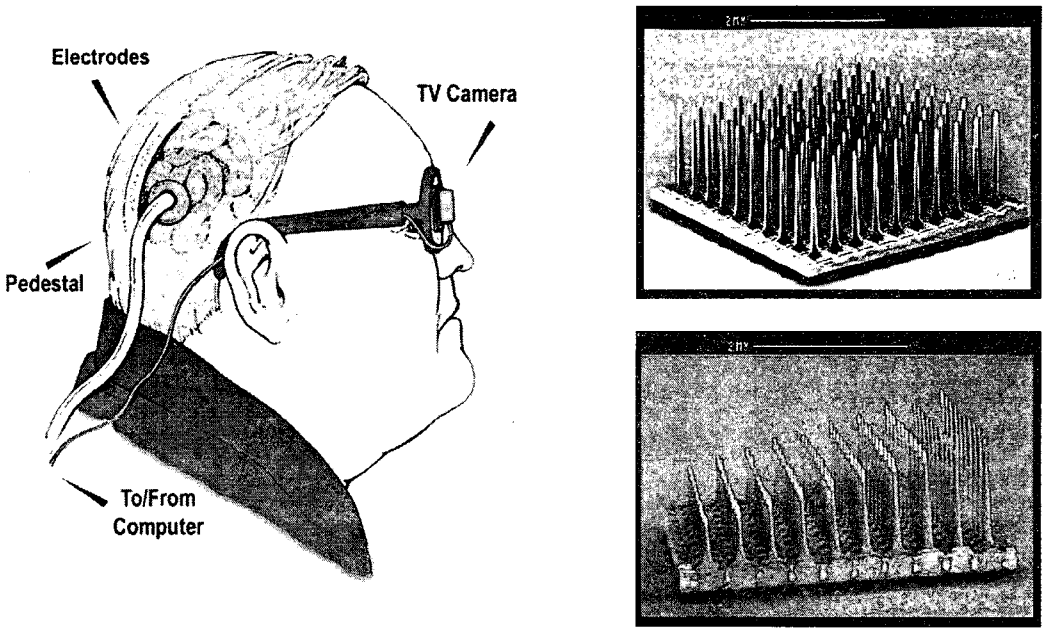

Fig. 1 Cortical implant of the Dobelle group:
Utah electrode array (top right), Utah slant array (bottom right)

2.2 Optic nerve implant

In 2001 Association for Research in Vision and Ophthalmology (ARVO), this group in Belgium reported on their attempt on one patient–59 years old volunteer with RP. They used a self-sizing spiral cuff electrode with 4 stimulation sites contacting through the optic nerve at four directions. Psychophysical experiments included a pattern recognition task. Fifty simple patterns were used during a ten-session program with feedback from the instructor. Result is that the performance improved regularly with practice with an increasing score and a decreasing delay to recognition. But, a low resolution artificial vision can be expected from the prosthesis after extensive training [5]. In 2002 ARVO, they compared optic nerve activation and related phosphenes. They had same volunteer who introduced in the 2001 paper was still in application. The only volunteer involved up to now describes phosphenes whose attributes (threshold, localization, luminosity and size) are modified by the stimulation parameters. The result is that phisphene size and position are very different from what could have been expected on the basis of the retinotopically activated axons in the optic nerve. So, they concluded the physiological mechanism encoding schemes to be investigated [15].

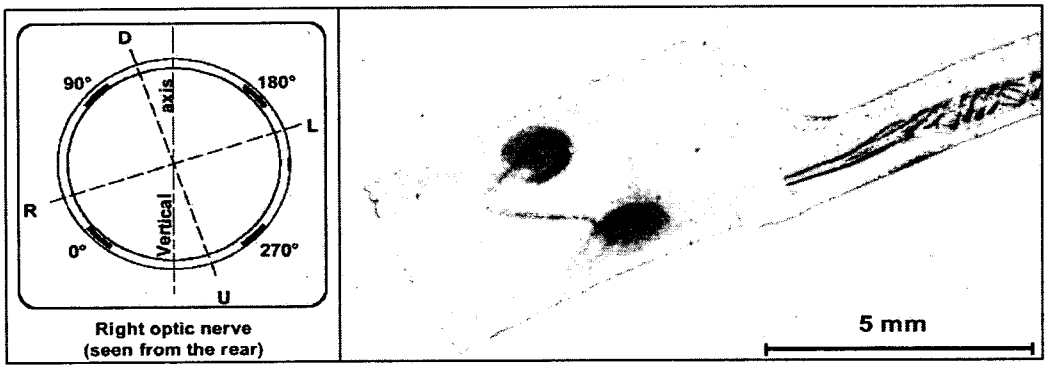

Fig. 2 Spiral cuff electrodes for optic nerve implant:
Cross-section view of electrode sites (left),
Magnified view of electrode (right)

2.3 Epi-retinal implant

2.3.1 MIT& Harvard

According to their report in 2001 ARVO, this intercollegiate team has done a feasibility assessment of the potential of retinal prosthesis. Five patients with RP and one with normal vision were studied with micro-fabricated electrodes. Data was obtained with stimulations performed over periods ranging from 80-265minutes. Response was judged to be reproducible if there was a similarity of the description of form elicited y an identical stimulus. The result was that normally sighted patient achieved this criterion 49% of the time, and three of five RP can 22-59% perception. Average accuracy was 41% and reproducibility 66%. Those results were not as expected, and they need to improve the stimulation methods and the subsequent studies [16]. More recently, they tried to use polyimide electrode as a sub-retinal method. They process an animal test with polyimide strip for physiological test only [17]. In addition to this new trial of other strategy, they introduce a trans-retinal implant. Trans-retinal implant is different from epi-retinal implant in the stimulating direction. Stimulating method of Epi-retinal implant is a parallel current compared to the retinal surface. Because two poles of bi-polar electrodes are both over the retinal surfaces, stimulating current path has the horizontal shape to the surface. Poles of bipolar electrodes of Trans-retinal strategy are remote between two. One is over the retinal surface, and the other is under the sclera. So, Vertical current stimulation is available. They compared with these two strategies of threshold, evoked cortical potential, etc. And they concluded Trans-retinal strategy is more effective than Epi-retinal strategy [18, 19]. They also researched the long-latency of responses of ganglion cell to the electrical stimulation [20]. Additionally, they examined the damage after vitreoretinal surgery [21]

2.3.2 Johns Hopkins University (JHU)

They have reported in 2001 about a real-time simulation in a head-mounted video display. Subjects were shown 4x4, 6x10, 16x16 pixelized live video images from a head mounted camera. All tests were done by 8 normally-sighted subjects using high contrast live images without pixel dropout or added dynamic noise. They concluded initial (4x4) epi-retinal electrode arrays are unlikely to allow useful vision to a prosthesis wearer beyond crude localization and discrimination, but 6x10 may allow spot reading and provide helpful visual support in simple object recognition and manipulation tasks. More complex search, orientation, and manipulation tasks are likely to require finer arrays of at least 16x16 electrodes [22]. More recently, they tried to reduce thresholds and further maximize stimulus parameters for a retinal prosthesis the effect of reducing the size of the stimulating electrode was studied in both normal and retinal degenerate(rd) isolated mouse retina. And they concluded that stimulation of the ganglion cell side of normal retina with an electrode of smaller diameter (25um vs. 125um) did not yield a reduction in stimulus thresholds, or a change in response latencies. And they expected further manipulation of stimulus parameters is necessary in order to reduce stimulus thresholds, and create a more favorable prosthesis [23].

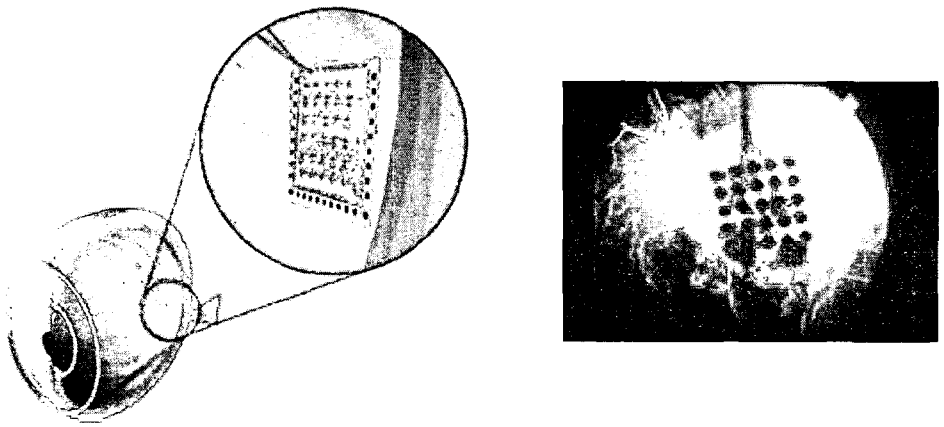

Fig. 3 concept of the JHU epiretinal strategy (left)
Photo of implanted electrode array by epiretinal strategy (right)

2.4 Sub-retinal implant

2.4.1 University of Illinois

In 2001, this group announced their results on the feasibility and safety test of implanting micro-photodiode based silicon chip retinal prosthesis into the sub-retinal surface. Three patients with RP and visual acuity of hand motions to light perception were each implanted. Artificial Silicon Retina (ASR) inserted as a part of an FDA-approved safety and feasibility study. They obtained results four months after surgeries, the patients suffered no discomfort. ASR was functioning electrically and has remained stable. They concluded that ASR retinal prostheses can be implanted into the subretinal space of at least some RP patients. But durability, long-term safety, feasibility and suitability of ASR are yet to be determined [24]. More recently, they announced ASR of moderate-term safety, feasibility and efficacy. Six patients received implants containing ASR chip. During 6 to 18 months with subjective interviews, ETDRS, automated visual fields, fundus photography / angiography and electrophysiology were followed. After experiments, they concluded that ASR can be implanted into the sub-retinal spaces of RP patients for at least 18 months and produce improved visual function. The longer-term durability of the ASR and its safety, feasibility, efficacy and suitability for the treatment of RP, are yet to be determined [25].

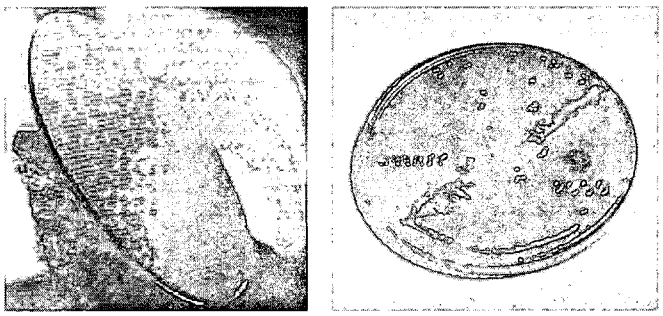

Fig. 4 magnified view of Artificial Silicon Retina^{TM} (left)
Real scale of Artificial Silicon Retina^{TM} (right)

2.4.2 University of Tuebingen

In 2001 , they announced the stimulus-related activity with multi-electrode recordings from the visual cortex of animals carrying sub-retinal implant. They defined feasibility of the sub-retinal approach is the correlation between characterization of neuronal activity of visual cortex and sub-retinal electrical stimulation. With 10 or 64 Pt-electrodes (on silcon foil) were chronically implanted in the skull above the dura mater in pigs. Repeated focal light stimulation of different size and position within the visual field was used. After this experiment, they concluded that sub-retinal electrical stimulation lead to an activation of the visual cortex with responses similar to those evoked by light. Those result support the feasibility of a sub-retinal visual prosthesis [26]. In 2002, they announced the safe surgical MPDA implant techniques on Animal tests. Those tests included variable vitrectomy on transscleral incision to decide the proper surgery [27-29]. In addition to that surgical techniques , they implanted MPDA under the cat retina. Then, they used Infra red 830nm laser on the MPDA. To obtain datum, they examined ERG on cats [30, 31].

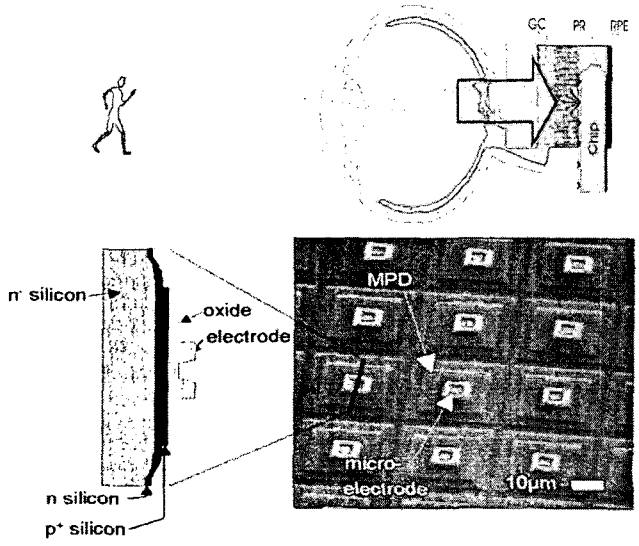

Fig. 5 Concept of the subretinal implant strategy in Tuebingen (top), PD integrated Silicon micro electro array and Its cross section view (bottom)

3. The Korean retinal implant project

3.1 Electrode & micro-tack

We made a polyimide based micro- electrode arrays (MEAs) for electrical stimulation and bio-compatibility test. First generation of the MEAs has a long percutaneous available shape with sites and pads in electrode structure (Fig.6). We used polyimide as the insulating material. Polyimide has some merits to choose. Polyimide has better insulation characteristic than Silicon oxide or Silicon Nitride, generally used in silicon fabrication process [32]. In addition to this insulation characteristic, it can do a role of supporting frame. Other conditions are as follows: Polyimide has a good property of adhesion on cells, silicon fabrication process also available, transparency makes a post-operation observation possible and elasticity can help inserting electrode structures into the body during surgery. That is why the polyimide selected as an insulation material.

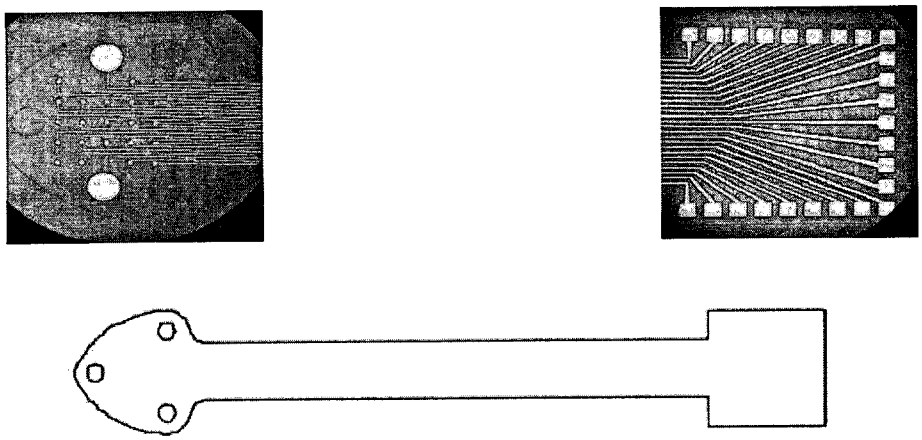

Fig. 6 SNU type first generation of polyimide MEAs

Electrode consists of three parts. Main part of the electrode is Triangular shaped head with Gold stimulation site integrated. Triangular shape has several advantages than other variable shapes. One is an economic usage of micro-tack. Micro-tack is a kind of nail to fix MEAs on the retina. Micro-tack is mechanically inserted into the retinal cell layer and penetrated through the sclera; it can cause local damage around the tack. Local damage can increase the number of glial cells, and these sequential effects result in the insensibility of stimulation. So, in Epi-retinal strategy, number of tack to fix is one of a critical factor. Triangular shape needs only three tacks at each side. Another advantage is an easy surgery. When surgeon inserts MEAs between the narrow layers of retina, acute angle can decrease the friction when he directs MEAs to the intended position. Besides, triangular shape closely adheres to the retinal surface better than Rectangular or Circular shape [33]. In addition to the triangular design, we made perforation holes to give some circulation path of body fluid between upper and lower side of MEAs. This increased the life time compared to when the array had none [34, 35].

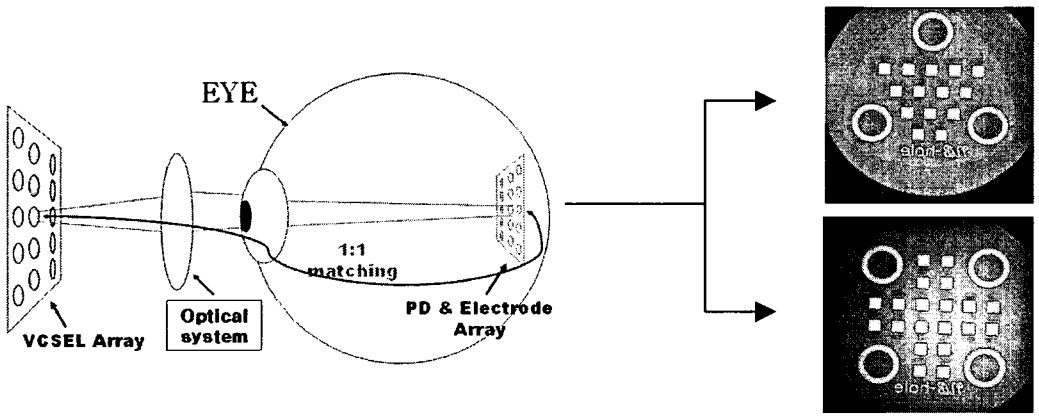

Fig. 7 concept of SNU type retinal Implant with PD integrated.
Expected Triangular shaped electrode (top right), rectangular (bottom right)

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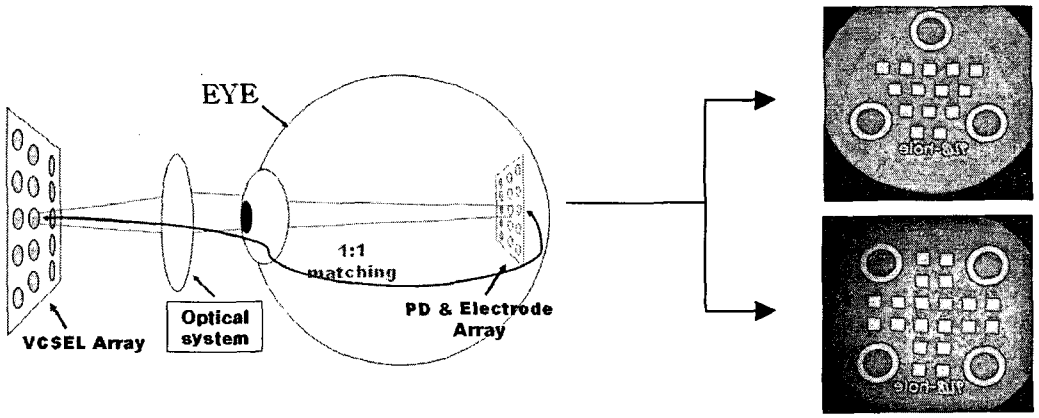


Fig. 7 concept of SNU type retinal Implant with PD integrated.
Expected Triangular shaped electrode (top right), rectangular (bottom right)

Final design includes PD's (Photo-diodes) integrated polyimide MEAs. In them, long metal lines and connection pads are not required. They receive optical signals using photodetectors which generates electrical current pass onto the retina. Fig. 7 is the schematic view of the MEA integrated with photodetectors.

3.1.1 Polyimide Fabrication process

Sequential Polyimide process is shown in the Figure below [33]. First, we deposited sacrificial oxide 3um-thickness. When we complete the fabrication, this layer will be removed and electrode structure separated from the silicon wafer. Next, polyimide(PI2525) is coated with 3000rpm spin speed after promotor VM651 processed on the surface. 3000rpm speed can make a 10um-thick polyimide layer. After this process, Ti/Gold/Ti (200Å/3000Å/500Å) is deposited by the E-Gun Evaporator. First Ti layer increases adhesion property between Polyimide and Gold, second layer. Second Gold layer is the site material. Third Ti layer will be a standard if metal sites are open or not. Because, Polyimide has a transparency, it is very difficult to decide whether last layer Polyimide (top insulation layer) is removed. So, we made a first mask as the Ti-protecting mask both on sites and pads. After first pattern, Ti can be removed by the 2% HF solution. Then, second mask used. Second mask has a role of Au line patterning include with sites and pads. After this patterning with Mask Aligner, we can remove Au with a solution, nitro-hydrochloric acid (Hydrochloric acid: Nitric acid = 4:1). Then, like previous process, remove Ti with 2% HF. Patterning of sites is completed when this sequence is done. Before next process, upper polyimide coating, all of photoresist(PR) used in the mask patterning must be ashed out. Proper methods are Acetone cleaning and PR-stripping with PR Asher. After complete removal, we can deposit upper polyimide with 3500rpm spin coating. This process can make a 6um-thick polyimide layer. After this process, 1000Å Ti must be deposited used as mask during Polyimide etching. Then, third mask is used. This can define the whole shape of electrode structure. Next, Reactive Ion Etching machine (RIE-80: generate O_2 plasma to etch) are applied to etch polyimide (O_2: 100sccm, RF: 100W, Pressure: 100mTorr). After this, sites and pads must be open. Lastly, 20% HF solution used to remove sacrificial oxide layer and separate electrode from silicon wafer. In this solution, some unwanted particles

on Ti can be washed out because Ti-upper coated on Au- removed completely. So, we can get clean Au surfaces. All of the sequential process can be seen at (Fig. 8)

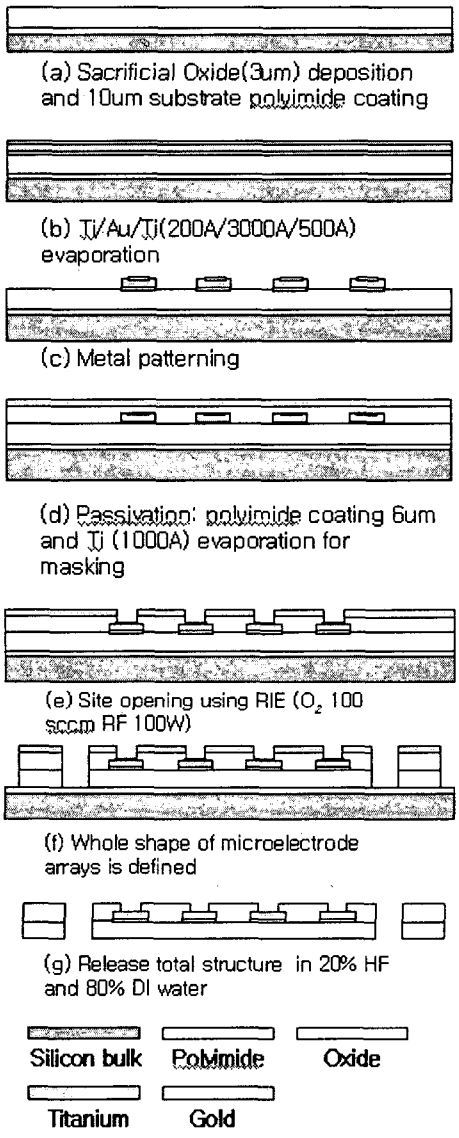


Fig. 8 sequential fabrication process for Polyimide MEAs

3.1.2 Micro-tack

When we direct Epi-retinal strategy, fixation on the retinal surface is a very important factor. One of fixing method is usage of micro-tack [11]. This can mechanically fix MEAs on the retina. Three types of micro-tack shape are designed. Three tack designs are categorized into two kinds of shape. One is 'barbed wire shape, the other is 'staple shape'. Barbed wire shape is divided into two: long barbed wire, short barbed wire (Fig. 9). Barbed type is made of silicon and coated with parylene. It has a spec of length 3 mm, width 300 ㎛, height 200㎛. High stability after insertion is a merit of this strategy. Staple type is made of silicon and not coated. It has a same spec as barbed wire shape tack. But, flexibility is a characteristic of this tack after insertion. Micro-tack has been commercially sold by Grieshaber Co. Inc., Switzerland and still in process. Their tack is made of Titanium and spec of length 2.5 mm, disk diameter 900 ㎛ tip diameter 300 ㎛. This tack has some defects: it is invasive to the membrane and tissues. Titanium tack must be made by hand with low yield and high cost. Silicon tacks are better in these regards. They can be made by silicon fabrication technology and guarantee higher production rate and variable shapes. They are shown with three different configurations in Fig. 9.

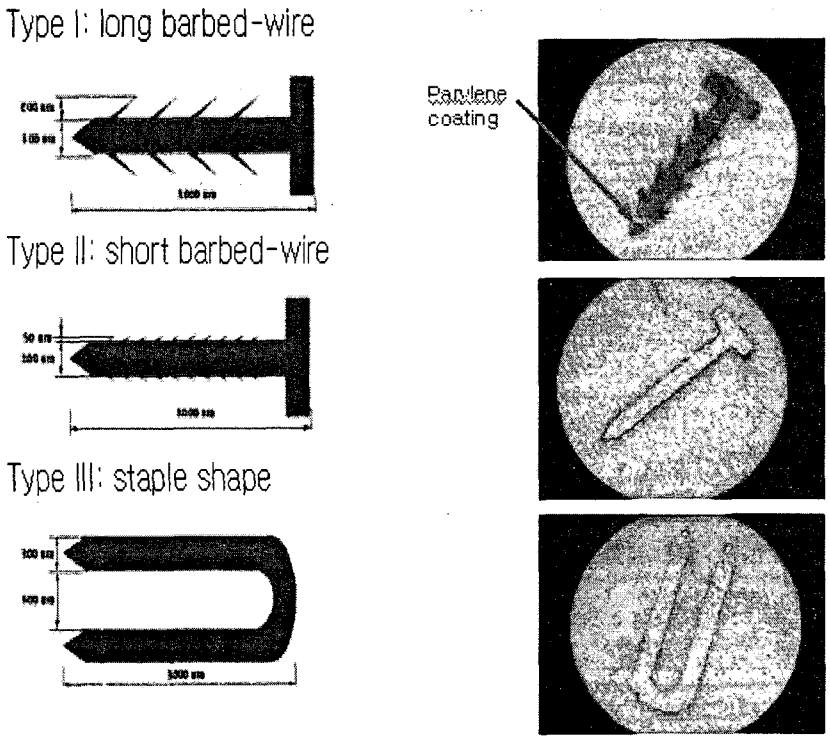


Fig. 9 variable micro tack design (left) and microscopic view after fabrication finished (right)

3.2 Biocompatibility test & cell recording

We experimented the biocompatibility test both In-vitro and In-vivo situation [36]. In vitro test was processed with three types of MEAs. Two kinds of conditions were applied. One is about perforation holes between electrode sites, the other is about electrode site opening. Target cell was human retinal pigment epithelial cells(RPE) , it was harvested from donated eye, our aim of this experiment was evaluating the adhesion and survival on polyimide electrode array. Each type of polyimide electrode array was placed in each well of 24-well plate and $1x10^{14}$ of RPE cells were plated on each well. The RPE cells were incubated at 37°C with 5% CO_2 for up to 4 weeks using 10% fetal calf serum and MEM culture media. During experimental period, photographs of RPE cell cultures were taken and microscopic examination was done after 5, 10, 15 and 20days to identify growth pattern, morphological change and viability. At day 8 and 24, RPE cells were harvested and counted Neubauer chamber using new methylene blue staining to identify abnormal proliferation or cell death. In the result, RPE cells grew on polyimide electrode array in a monolayer after 10days, and showed good affinity to polyimide electrode array and exposed gold electrode. After 10 days, they showed contact inhibition. There seemed no abnormal morphological changes or no piled-up growth. In case of cell counting, it increased on 8^{th} day and on 24^{th} day (harvested and counted). There were 5.9~11.7% of dead cells. There was no difference in the live cell count of control well and of well with polyimide electrode array on day 8 and on day 24. Fig. 10 shows this result. Fig. 11 is a magnified view of cell cultured MEAs on day 13 and on day 20

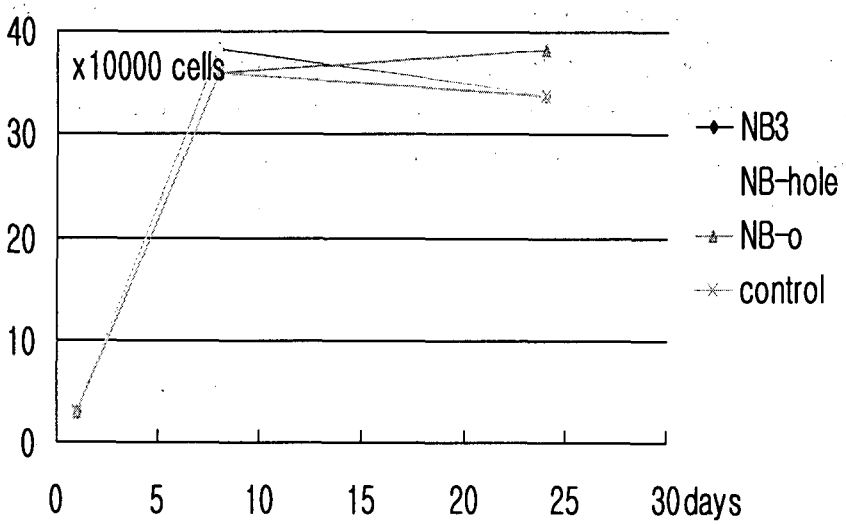


Fig. 10 Number of cells on the MEAs of variable options:
NB3: no holes, sites closed, NB-hole: holes, site closed
NB-o: no holes, site opened

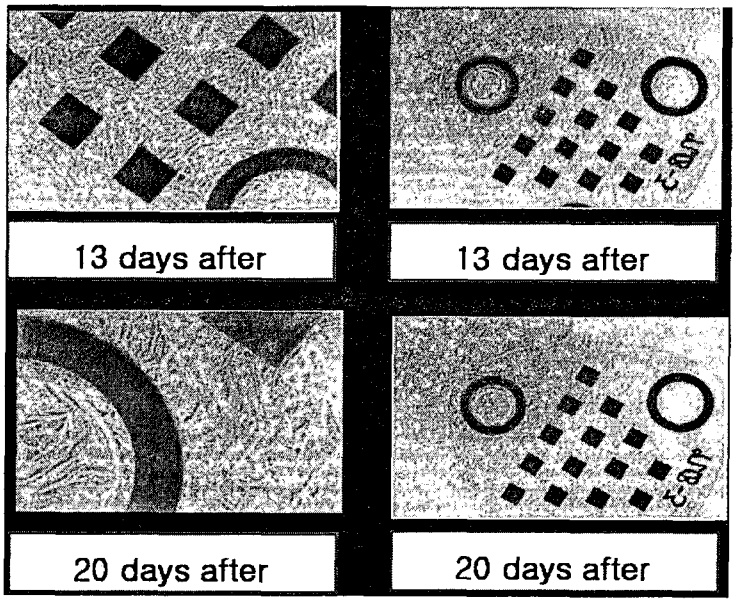


Fig. 11 biocompatibility test of Polyimide MEAs for short term

For the in vivo test, pars plana vitrectomy was done in 5 white rabbits [37]. The right eye of each rabbit was used for the test and the left eye was kept intact for the control. After vitrectomy, polyimide electrode array was curled and inserted into the eyeball through sclerotomy site. In 2 eyes, polyimide electrode array was stretched and fixed with retinal tack on the retinal surface or visual streak. In another 3 eyes, polyimide electrode array was not fixed and kept in freely floating state in the vitreous cavity. After 1,2,4,8 and 12 weeks, the inflammatory change or other complications in vitreous and retina were evaluated. On 8^{th} week, electroretinography(ERG) was checked in operated and control eye. After 12 weeks, the eyeballs were enucleated and histological change of retina was evaluated under HE stain. The result was as follows. Polyimide electrode array did not induce haziness or inflammatory change of vitreous until after 12 postoperative weeks. Dissection of eye also confirmed that there was no retinal detachment, vitreous haziness, no cataract change in free-floating polyimide electrode array implant group and fixed polyimide group (Fig.12). And there was no histological difference between control and operated eye. There was no evidence of retinal neural cell loss or inflammation on microscopic examination (Fig.13). ERG also showed no difference between the transplanted eye and the healthy eye for control value (Fig.14). We concluded that the polyimide electrode array showed good affinity to RPE cells and did not harmful effect. And it also showed very good stability and safety in rabbit eye by 12 weeks. This can support the possibility of using polyimide MEAs in human organ. To clarify the possibility, additional tests are still in process.

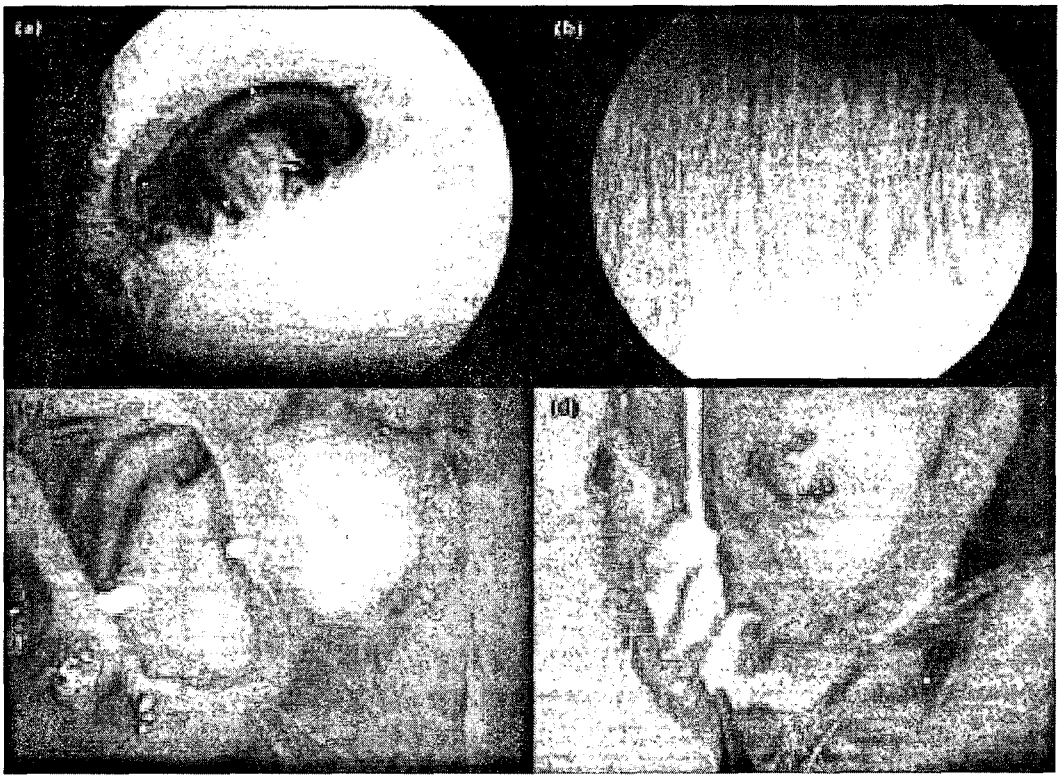


Fig. 12 histological observation of rabbit eye :
(a) Polyimide MEAs on the rabbit retina seen through the transparent eye
(b) Rabbit retina (c),(d) implanted Polyimide MEAs

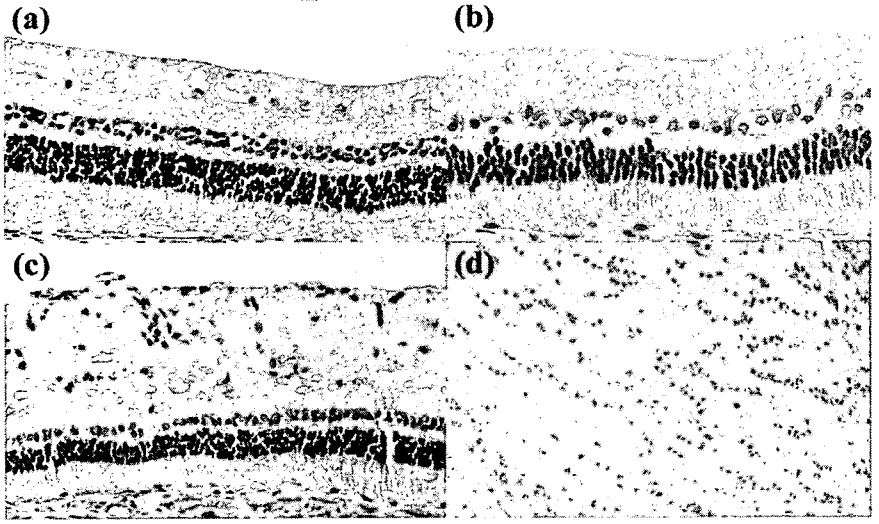


Fig. 13 Cross section views of rabbit
Retina to measure damage or degeneration by implantation

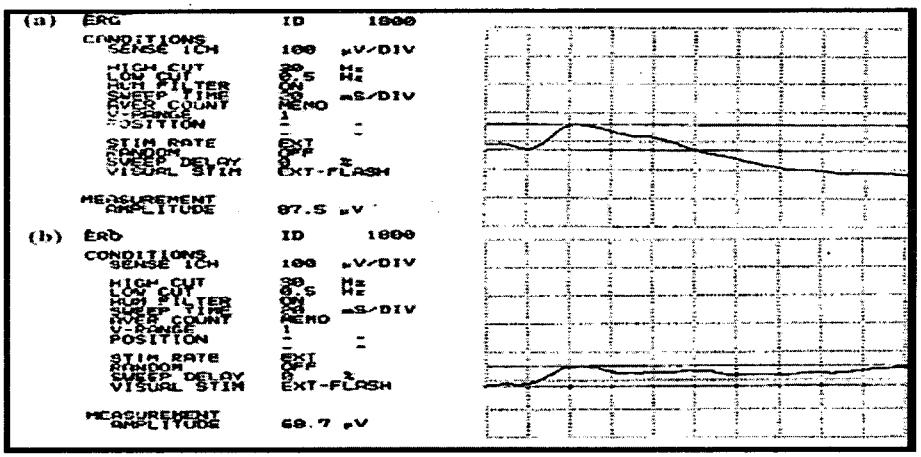


Fig. 14 ERG measurement to detect a retinal function

3.3 Retinal Electrophysiology

With the biocompatibility test, Electrophysiological test is also important. Goal of this research is to decide the stimulating parameters that are proper to retina. At present, we use Rabbit retina as a subject, and record its response with Multi electrode array (MEA) [38]. Recording is still in process.

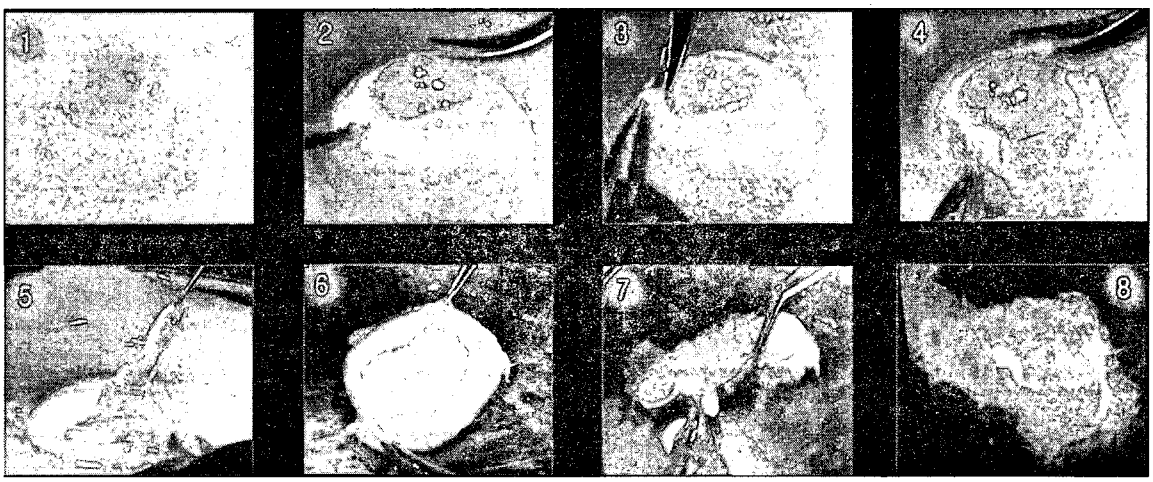
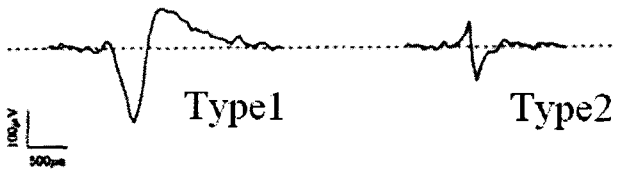


Fig. 15 sequential process of rabbit retina preparation on the chamber plane

Fig.(15) is a sequential process of retina whole mount preparation on the plain plate. First, we injected sodium pentobarbital (1ml/kg) for sedation. Then, we cut of carotid artery to sacrifice the rabbit. After this process, we get eyeball from the rabbit. Next, we remove front portion of eye (cornea, iris, and lens) and the vitreous in ACSF solution. Then,

separate retina from sclera. Number 5 of the Fig. 15 means this state. Now, we have to place retina into the chamber and perfuse ACSF continuously. When we finish this step, retina preparation is all done. Now, for 3-4 hours, we can record response from the plain retina. Retinal Ganglion cell activity is as follows.



(Grumet et al, 2000; J. Neurosci. Meth. 101: 31-42)

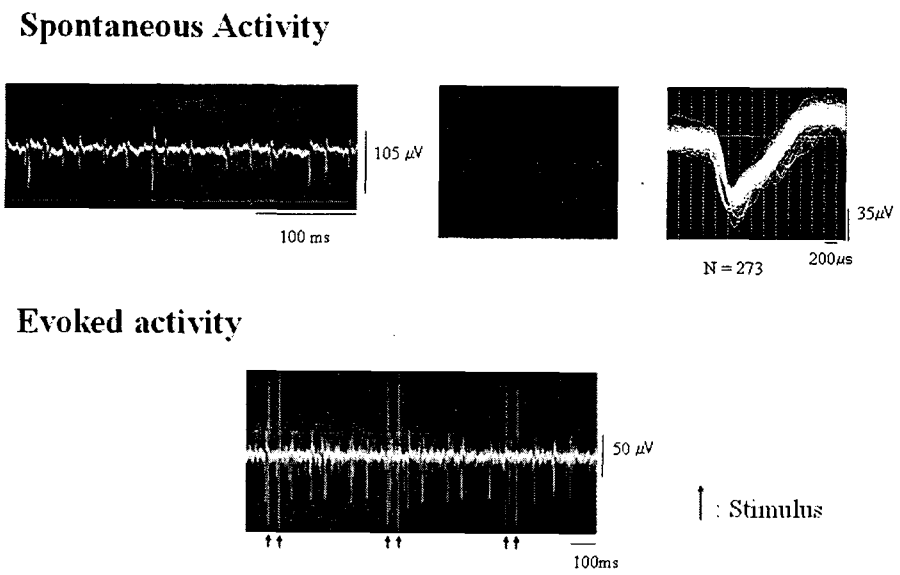


Fig. 17 Measurement of Electrophysiological activity of stimulus
Type1 and Type2 (top) means a spontaneous discharge of rabbit ganglion cell

3.5 VCSEL - mediated optical link

We send processed signal through telemetry. Because Eye ball has its characteristic pressure and must not be contaminated, telemetry is an important factor to consider. Signal processing chip is not yet defined, but we are researching the optical link as a transfer source. At present, optical source 'Vertical Cavity Surface Emitting Laser (VCSEL)' is taken into consideration. VCSEL is a new kind of semiconductor laser that is already having a dramatic influence in computing and networking, sensing and other applications. VCSEL has several advantages than other optical devices [39]. First, VCSEL is simple. Because silicon fabrication process makes VCSEL integration into small sized arrays, one to one connection between VCSEL and PD are possible. This can remove a de-multiplexing stage. In addition to this concept, VCSEL permits a co-transportation power & signal. This is why the VCSEL process is simple. Second, VCSEL is independent to electromagnetic field. VCSEL source is laser, field effect is not considered during transportation. At present we are simulating this laser source through simulation tools to obtain parameters of power, current, etc [40].

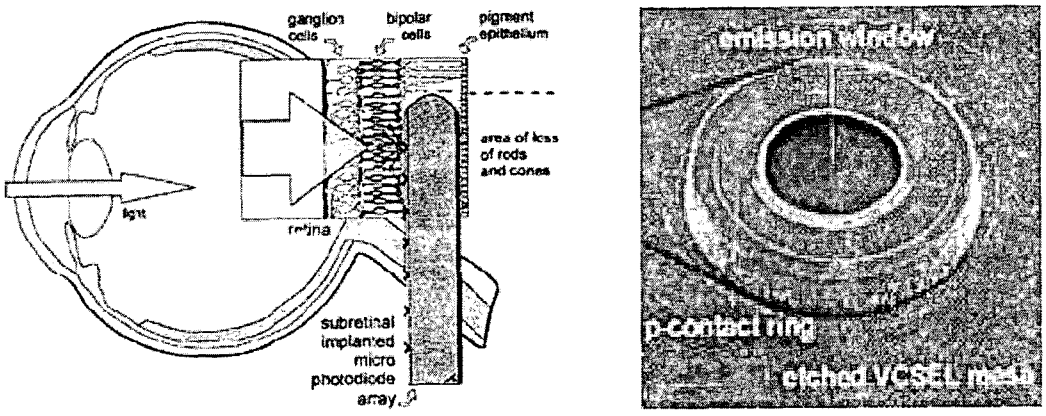


Fig. 18 concept of the subretinal implant strategy using VCSEL as laser source: magnified view of VCSEL structure (left)

4. Summary

In this paper, we introduced a retinal implant (both Epi- and sub-retinal available). We introduced worldwide efforts to make artificial vision systems. We have outlined our approach to this problem. The SNU artificial retina system uses polyimide based microelectrode arrays integrated with photodetectors. Direct stimulation of neurons by the photogenerated electron carriers are attempted using vertical cavity surface emitting laser arrays.

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