Flexible Electrode Array for Retinal Stimulation

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Abstract :

In this Work, ITO/PET (Indium Tin Oxide / Polyethylene Terephthalate) electrode structure which provides biocompatibility, mechanical stability and flexibility is fabricated. Flexible ITO/PET implantable electrode array for a retina has been developed. The electrode array is fabricated on a thin PET/ITO substrate and is encapsulated using, SU-8, an insulating material. PET substrate and SU-8 polymer make electrodes flexible so that they could shape to contoured tissues. A layer of gold on the stimulation sites serves to reduce the electrode/tissue interface impedance. Prototypes of 4×4 and 12×6 electrode arrays are fabricated for primary and dense configuration of retina prosthesis respectively. The exposed electrode diameters are 125µm for primary and 100µm for dense micro electrode array. The stimulation sites of primary configuration were connected via 50µm interconnects with 50µm spacing. 40µm width traces with 15 µm spacing connect sites to bonding pads in the other design. To verify the functionality of the micro fabricated electrodes, the electrochemical impedance spectroscopy is measured. The electrode/tissue impedance was 19.4KΩ at 1 KHz for 7854µm^2 area.

Keywords: Retinal Prosthesis, Microelectrode Array, Stimulation Site, Flexibility, Biocompatibility, ITO/PET substrate, SU-8.

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1. Introduction

Retinitis Pimentos (RP) and Age-Related Macular Degeneration (AMD) are two of the most common retinal diseases. Both these diseases stem from a progressive loss of the photoreceptor cells, eventually leading to complete blindness [1]. Fortunately a large percentage of the neural cells connected to the photoreceptors remain viable, and electrical stimulation of these cells has been shown to result in visual perception [2]. Therefore, people try to restore visual function by using retinal prostheses to stimulate bipolar or ganglion cells in the retina [3].

The micro electrode array is a component of a retinal prosthesis. This array will serve as the interface between an electronic imaging system and the human eye, directly stimulating retinal neurons via thin film conducting traces. Because the array is intended as a long-term implant, biocompatibility and mechanical strength requirements must be met. This is vital to minimize stress and prevent physical damage to the retina. Also, the device must be robust to withstand the forces imposed on it during fabrication and implantation. However, a significant disadvantage of the retinal prosthesis is that the curvature of the retina makes chronic lodging of the electrode array at the correct position difficult [4].

In order to promote injured or sick nerves for the restoration of function, scientists have developed chronically implantable microelectrodes to record from and/or stimulate cells of the remaining nervous system. Partial restoration of lost function has been achieved by advances in functional electrical stimulation [5].

Typically, the electrode sites are made of a conducting metal deposited on a silicon-based substrate. Microelectrode is usually insulated by a passivation layer, leaving the electrode sites and bonding pads exposed [6]. Silicon microelectrodes show good biocompatibility and have the advantage of being compatible with CMOS-based on-chip signal conditioning circuitry [7]. The main problem in silicon-based micro electrodes is that the silicon substrate is mechanically rigid and brittle; therefore if the electrode moves spontaneously, it may cause severe damage in tissue. Therefore for accommodation for movement, a flexible electrode is highly operational in implantable micro electrode arrays.

The main approach for flexible electrodes is polyimide-based electrode which has drawn widespread attention [8]. In 1992, Boppart presented a first flexible electrode [9]. The research in this field then followed by more advanced designs by Gonzalez [10] and Weiland [3].

A new approach for flexible implantable electrode has been presented in this paper using ITO/PET. Among the flexible electrodes, ITO/PET electrode combines good biocompatibility [11], proper mechanical characteristics, high dielectric strength and is well known in micro fabrication. An ITO/PET electrode structure which provides biocompatibility, mechanical stability and flexibility is designed and fabricated in this work. A retinal implantable electrode and an electrode array for stimulation and recording from spinal cord have been fabricated with ITO on PET substrate. Although ITO is very biocompatible but it has relatively high impedance in contrast with other conductors like gold, therefore a layer of gold was evaporated on electrode sites for reducing electrode tissue interface impedance.

2. Micro fabrication

Used material for microelectrode array fabrication should have biocompatibility and flexibility properties. In this work, PET was used as a flexible substrate during array fabrication. The PET/ITO sheets supplied by Aldrich Company, in 100nm layer of ITO coated upon 127μm thick substrate of PET. The transparency of ITO/PET sheets is in the range of 75–80 % and they have a measured sheet resistance of about 45 Ω/square. Process flow of fabricating the flexible microelectrodes is shown in Fig. 1. Since the designed electrode has many thin parallel interconnects and the used substance (PET/ITO) is transparent, patterning the electrode structure on the substrate needs a photo mask with high accuracy. Therefore both a positive and a negative photo mask are made by glass. Before the fabrication process is started, it is necessary to wash and dry the surface of ITO to increase the possibility of coherence photoresist on the substance. Thus, the substance is immerged in a 2% soap solution in 60°C for 10 minutes. Then, it is putted in ultrasonic for 5 minutes, washed by distilled water, putted in ultrasonic for 5 minutes and putted in 99% acetone subsequently. For the last preparation step, the substance is immerged in 99.5% heated methanol till 60°C in ultrasonic for 5 minutes and finally cleaned by 99.7% isopropanol at 60°C in ultrasonic for 5 minutes. The substrate is ready now for starting the fabrication process as it is showed in step 1 of figure 1. The second step is covering the surface of ITO by photoresist. By using of spin coating method and in 3000rpm speed a thin and defect free layer of photoresist covers the ITO; the thickness of photoresist layer is 1.4μm. The photoresist, which is used in this step, is a positive type and belongs to Shiply Company. For soft baking, the sample is putted in oven at 90°C for 20-30 minutes. The next step is aligning and exposing that causes the electrode design is patterned on photoresist layer. So, by an mask aligner, the sample is exposed the 350 watt ultraviolet waves for 30 seconds. For creating the electrode structure on photoresist layer, it needs developing. Thus the sample is immerged in 4.5gr/lit NaOH solution for 60-70seconds and then washed by deionized (DI) water and dried (step 3). The sample is putted in oven at 90°C for hard baking to be prepared

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for etching. In step 4, the purpose is eliminating some parts of ITO according to created pattern on photoresist layer, so the sample is immerged in etching solution that includes 37.5% HCl and distilled water by 1 to 1 proportions for 30 seconds. At the end of step 4, the electrode structure patterns on ITO, so in step 5 the sample is immerged in acetone to eliminate the photoresist layer and washed by distilled water and dried. One of the most important features for the electrode arrays is electrical impedance that obtains of interaction between stimulation sites and tissue. Therefore, for improving this feature, it is vital to use of low impedance material for stimulation sites. As it is mentioned above, gold has low interaction impedance in comparison with ITO and also is biocompatible, so in following fabrication process a layer of gold is coated on stimulation sites. In step 6, the sample is putted in evaporation machine to cover a layer of gold on the surface of sample. At the end of this process a 99.999% gold layer is created with 170nm thickness. The needed pattern of gold on ITO is prepared by gold etching process. For this process, as it is cited in step 7, a layer of positive photoresist covers the gold surface as it is explained for step 2. Soft baking and aligning and exposing and developing are the next steps, which are done as they are explained before. At the end of step 8, a layer of photoresist covers both stimulations sites and interconnecting pads. Step 9 is gold etching that the sample is immerged in KI and I_2 solution for 70-80 seconds. In step 10 the sample is washed by acetone to eliminate photoresist and then it is washed by DI water and dried.

To passivize the electrode array and ensure biocompatibility, the electrodes were coated by an insulating material, SU-8. The polymer SU-8 was chosen because of its excellent lithographic properties. It also provides biocompatibility and flexibility features for the passivized electrodes [12, 13]. Since one of the important features of this microelectrode array is its flexibility, the amount of flexibility of SU-8 and the used substrate should be approximately same. Comparing the young's modulus of SU-8, which is 2GPa, and PET substrate, which is 2.2GPa, confirms passivation layer does not reduce rate of flexibility. Therefore, in step 11, a layer of SU-8 covers the surface of sample. This layer, which is created by spin coater in 3000 rpm speed, has 2µm thickness and needs 30 minutes soft baking in oven at 95°C. Because SU-8 is a negative photoresist, for aligning it needs a positive photo mask. After aligning, the sample is exposed by UV for 60 seconds. After exposing, the sample is hard baked for 15 minutes at 95°C. The last step is developing that the sample is immerged in SU-8 developer. Consequently a microelectrode array is fabricated that has golden sites and pads and a passivized layer that is opened on sites and pads.

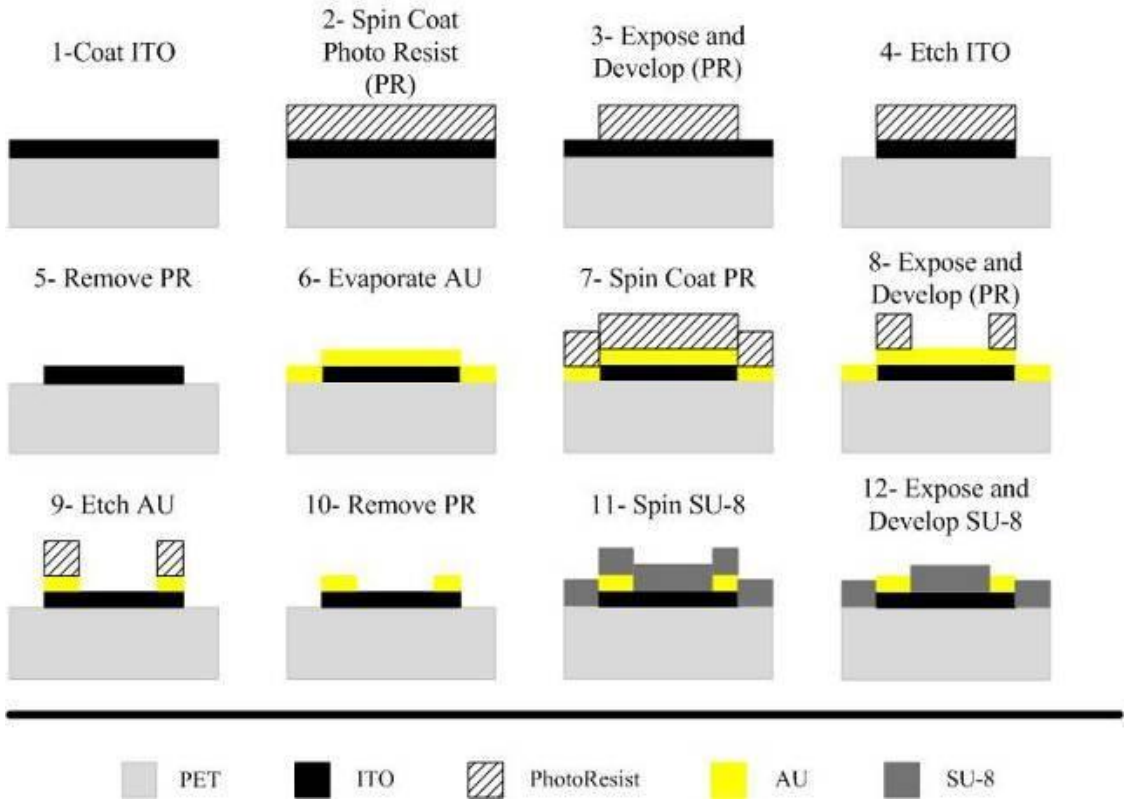


Fig. 1. Process flow of ITO/PET microelectrode Array fabrication.

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3. Results

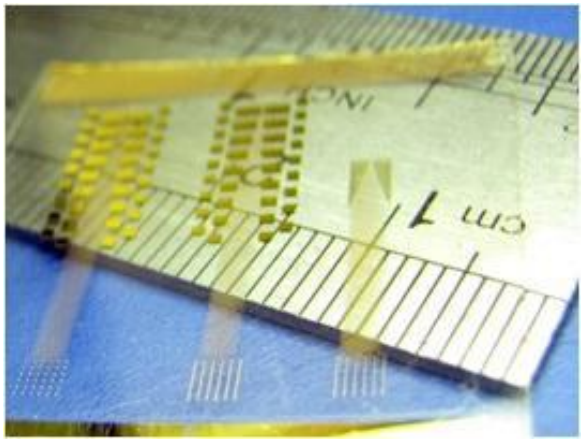
Retinal microelectrode array

Retinal prosthesis stimulation electrodes are micro fabricated in two prototypes. The primary prototype, consist of 4×4 stimulation sites with 125µm diameter and 250µm center to center spacing between stimulation sites. Interconnects with 50µm width connect the sites to bonding pads with spacing of 50µm. Figure 2 shows the microscopic view of stimulation sites. Since the substrate is transparent, some scratches that are created during the process on behind of the sample are seen in figure 2. This microelectrode array is the first sample, so for the next prototype, figure 3, these scratches do not exist anymore.

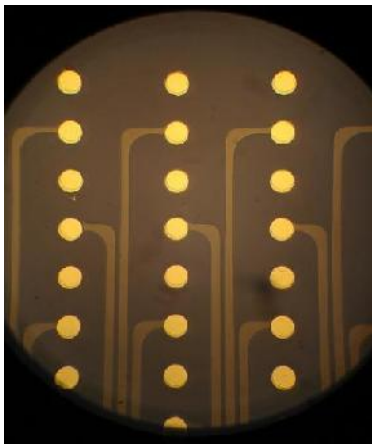


Fig. 2. 12 of 16 stimulation site of visual prosthesis electrode array taken by electron microscope.

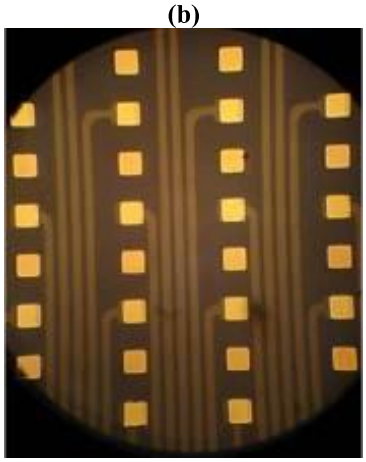
Because an efficient visual prosthesis needs high stimulation site, at the next step, number of stimulation sites is increased. The size of retina and available technology are two factors that cause some limitations on micro electrode structure. For next generation of electrode array, the number of sites is increased while both diameter of stimulation sites and width of interconnections are decreased. High density prototype consists of 72 (12×6) sites with electrode diameter of 100µm, and the 200µm pitch. Traces with 35µm width and 20µm spacing will connect sites to bonding pads (figure 3(a)). As it was mentioned, due to high impedance of the ITO/tissue interface, the electrodes were covered by gold. Figure 3(b) shows the microscopic view of stimulation sites covered gold. Stimulation sites are designed and fabricated in two shape, circle and square (figure 3(b, c)) in order to study results of stimulation by which of them is better. As it is explained in fabrication process, the whole of electrode array is passivized by SU-8 polymer, but there are openings in stimulation sites and connection pads, which are covered by gold.



(a)



(b)



(c)

Fig. 3. (a) Fabricated biomimetic microelectrode array with 72 sites 100-µm-diameter electrodes with ITO on PET substrate (b, c) stimulation sites of visual prosthesis electrode array covered with gold, circular

The electrodes inserted and remained in rat plasma for three days to test for protein absorption and thirteen days for stability. Electrodes showed resistance to body solvents and maintained the original shaped and properties. The young modulus of PET is 2-2.7GPa that shows high mechanical stability and flexibility. These electrodes also recover to their original shape

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even after rolling or folding as it is shown in Fig. 4. This feature causes this electrode array can curve easily as retina shape that it is the most beneficial of this electrode between others that are mainly based on silicon substrate.

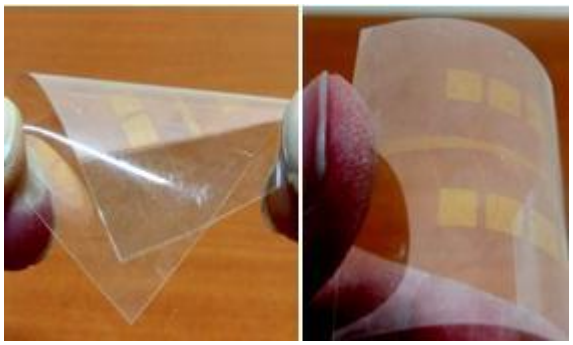


Fig. 4. An implantable electrode array for retina stimulation microsystem. The electrode can be folded and rolled and still maintains the original shape.

4. Test of Electrical Characteristic

Impedance evaluation has become a common method to non-invasively determine the electrical continuity and condition of chronically implanted microelectrodes in-vivo. Since electrophysiological saline solution is the primary constituent of body fluids, it is generally assumed as the impedance-testing environment in-vitro [14]. The fabricated microelectrode was mounted onto a printed circuit board (PCB) using epoxy. The stimulation sites were immersed in the saline solution and the test electrode pads was connected to the LCR Meter. Figure 6(a) shows diagram of the impedance test.

With this experimental set up, the electrical impedance was measured from 100*Hz* to 100 KH*z* frequency with a sinusoidal signal of 0.2V in amplitude at room temperature. The metal electrode/electrolyte equivalent circuit model is illustrated in Figure 6(b).

The electrode/ electrolyte interface is modeled with two parallel elements (R_E, C_E) which are series with the electrolyte resistance (RS).

The impedance of electrode-electrolyte interface depends on the species of metal, the type of electrolyte, and the surface area. The impedance decreases with increasing frequency due to capacitance component, while phase angels increases from -80 to -10 degree.

The electrode surface area and impedance shows an inverse relationship.

All the mentioned tests carried out on electrodes with gold covered stimulation sites. As expected, the measured impedance for the gold sites is substantially less than the impedance of ITO sites. The impedance characteristics have shown in Fig. 7 before and after metallization for stimulation sites of 7854µm^2 (a) and 3mm^2 (b) areas.

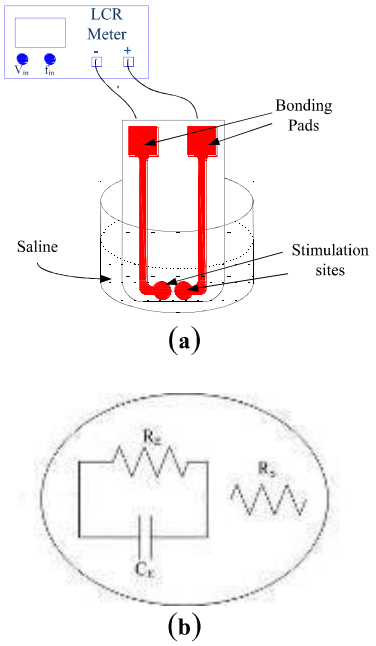


Fig. 6 (a) Impedance test diagram, (b) equivalent circuit

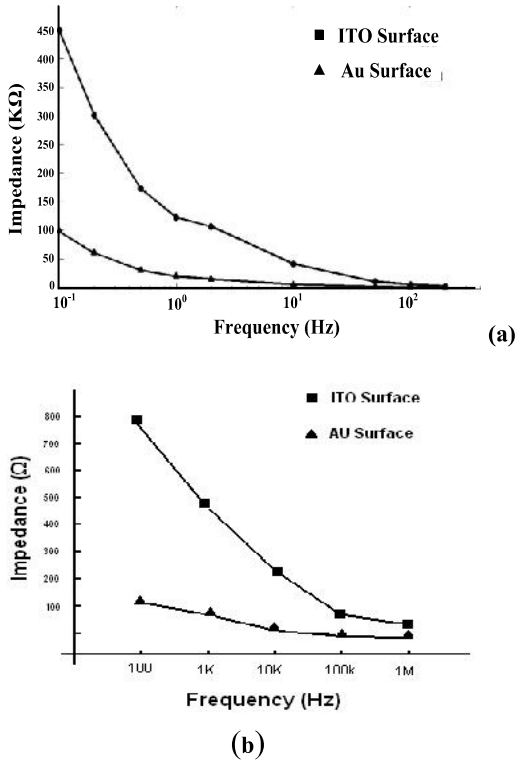


Fig. 7. Impedance characteristics of ITO and gold stimulation sites, (a) 7854µm^2 contact area, (b). 3mm^2 contact area.

5. Experimental Test

Besides the in-vivo test for measuring interaction impedance, the electrode array is tested in-vitro to study its biocompatibility. First, the electrode array

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was prepared for surgical implantation. It is important to the top of electrode be sharp as much as possible to be able to penetrate into the tissue. The next issue is guiding doctor during the surgical implantation as he is able to see the direction of electrode movement in eye. Therefore, as figure 8 shows, an LED was installed on the end of electrode for the tip of electrode distinction during implant surgery. Since the ITO/PET substrate is transparent, the electrode array can guide LED light.

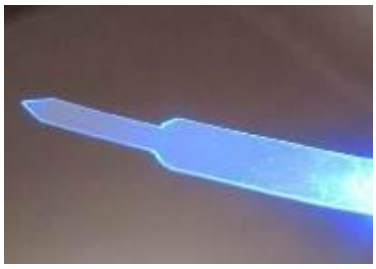


Fig. 8. Prepared electrode for surgical implantation

This electrode array has been implanted in a rabbit eye at Farabi hospital. Doctors were satisfied by the flexibility and mechanical stability of the electrode that was implanted on rabbit retina. After three months, the rabbit had been tested for possibility of infection creation. Fortunately, the test results did not show any infection for tested rabbit, which confirms the electrode array materials are bio compatible.

6. Conclusion

Flexible microelectrode array for retinal stimulation has been presented. Theses implantable electrode has been fabricated by biocompatible and flexible materials and it is expected that these electrodes reduce the tissue damage of non-flexible electrodes after surgical implantation. Also a flexible electrode would contact the tissue according the subject tissue form and shape, which is essential for proper stimulation. The PET/ITO electrodes provide safe contact while obtaining low resistance of equivalent electrodes by coating the stimulation sites with gold

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