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INVESTIGATION THE ROLE OF CARBON NANOTUBES FOR HIGH RESOLUTION VISUAL PROSTHESES

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Abstract- The subject of development of visual prosthesis systems for eliciting the visual restoration in people who lost their loss of vision has been searched for long years. Nowadays, several important visual prosthesis systems are being tested clinically with the developments in micro-technology and bioengineering fields. Aim of studies in this field is to increase the resolution for systems that can even read small letters, move without assistance, and sensitively recognize faces. While systems developed with the common metal electrodes have some restrictions in terms of increasing the resolution, carbon nanotubes (CNTs) are highly superior due to their electrical and chemical properties. In this study, CNT structure is discussed to increase the resolution in visual prosthesis systems and studies on the usage of CNT in microelectrode arrays, which are contact with targeted nerve tissue, are reviewed. Consequently, it is concluded that CNT can be used in visual prosthesis in order to increase the resolution after necessary clinical studies about biocompatibility, toxic effect, durability of CNTs that has high electrical conductivity, chemically inert structure and high aspect ratio, under long-term stimulation and recording are performed on animal and human subjects in detail.

Keywords: Carbon Nanotubes, CNTs, Electrode Tissue Interface, Visual Prosthesis, Microelectrode Arrays.

I. INTRODUCTION

Even if some regions in visual pathway are damaged in people who lost the ability of sight due to diseases such as Retinitis Pigmentosa (RP), Age related Macular Degeneration (AMD), glaucoma, some parts have remained intact. Although these diseases cannot be treated fully, even if there are approaches like transfection of genes encoding for light sensitivity in intact neurons [3] or neurotransmitter releasing mechanism [4], the largest number of clinical experiments completed or ongoing are in visual prosthesis field with developments in bioengineering and neuroscience. Visual prosthesis is a new and promising approach for visual restoration in people with degenerative eye diseases. This term can be defined as any devices that provide little light spots, called phosphenes, by bypassing the degenerated nerves in visual pathway and electrical stimulation of intact nerve cells.

The principle underlying the visual prosthesis system is to elicit visual perception with electrical stimulation of the remaining nerve cells without using the impaired layers in visual pathway. Visual prosthesis may be named according to anatomical location principle which targets to stimulate, like retina, cortical and optic nerve prosthesis. The first reports are related to cortical stimulation for providing phosphene perception. Nowadays visual prosthesis reaches to a level that can clinically restore the basic visual functions using different parts of visual pathway.

Retina prosthesis is placed inner or outer surface of the retina, so they are called epi-retinal or sub-retinal implant, respectively. Each position has unique engineering and surgical advantages and deficiencies. It has been showed in various studies that interface between living tissue and electronics implanted is functional and bidirectional [5]. Neuro-electric interface for visual prosthesis devices, which are expected to work for many years, should have a multi-functional and electrically conductive architecture.

Microelectrode Arrays (MEAs) produced on rigid substrate commonly used at interface has limitations on the number of electrodes. Electrode arrays are generally two-dimensional and its surface has a flat structure, but it cannot provide an efficient interface with tissues. Young's modulus of tissues is about 6 times less than that of metal electrodes, that is mechanical durability of tissues is 6 times weaker. This leads to serious mechanical incompatibility between stimulation electrode arrays placed into eye and tissue [6].

Reduction in electrode size is limited with increasing impedance. Increase in impedance leads to a decrease in Signal to Noise Ratio (SNR), so this situation is not preferred for recording step. In addition, it requires higher charge density. To handle challenges mentioned electrode arrays which have high charge injection limits, effective surface area, three-dimensional structure should be used. Intensive studies trying to solve these challenges bring about the approach of solving these problems with new materials. Carbon Nano-Tubes (CNTs) have attracted great attention thanks to their high electrical conductivity, chemically inert structure and high aspect ratio owned naturally [7].

Minimum current required to provide cell reaction is called stimulation threshold. This means in healthy eye that the signal is received from previous neural unit and delivered to ahead. Live tissues that are used for neural stimulation applications have their own damage limits. Applying stimulation beyond this damage limits will cause neural injury. Similarly, there is a point, which is defined as charge injection limit.

This is maximum amount of charge that an electrode can safely apply. The current needs to be higher than stimulation threshold. The highest current that can be applied depends on stimulation electrode charge injection limit and tissue's damage limit. Whichever is lower, the current must not exceed, as shown in Figure 1.

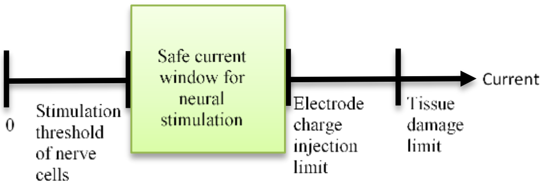

Figure 1. Limitations for neural stimulation

In this study, carbon nanotube structure is examined in stimulation electrode arrays in terms of increasing spatial resolution in visual prosthesis, studies in literature are reviewed, and role of CNT which is a promising material for neural interfaces in solving the problems encountered which include increasing the electrode number in stimulation electrode array is investigated. The most important limitation of microelectrode arrays used nowadays is large electrode size. Because small electrode size minimizes tissue damage and provides localized recording and stimulation, high resolution can be provided. Increasing in spatial resolution of visual prosthesis enables face recognition, moving freely and reading small letters correctly, as shown in Figure 2 [8].

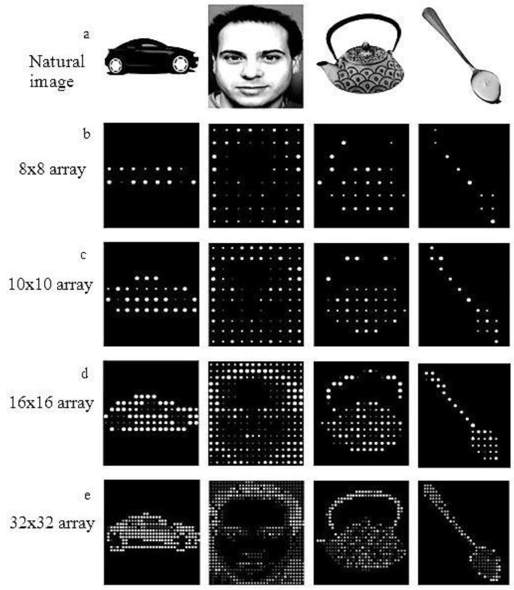

Figure 2. Simulated images of ordinary objects in phosphene map [8]

II. PROPERTIES OF CARBON NANOTUBES

CNTs are hollow cylinder in shape of graphite sheet. They are generally examined in two main categories. First of them is single-walled CNTs (SWCNTs) having the simplest form ranging in diameter of 0.3-2.5 nm and in length of a few millimeters. Other category is multi-walled CNTs (MWCNTs) whose diameters range from 2 to 100 nm and lengths range from 1 to 200 μm and formed coaxially interpenetrating SWCTNs [9]. Additionally, MWCNTs include concentric SWCNTs with interlayer distance of 0.34 nm [35]. Figure 3 shows carbon nanotube structure atomically.

While SWCTNs have metallic or semiconducting feature, MWCNTs may exhibit metallic feature [10]. Electrical conductivity of CNTs depends on diameter, number of graphene walls and chirality. Chirality is a term that is used for the sequence of atoms in grapheme sheet in shapes such as armchair, chiral and zigzag. CNTs may be produced from a catalyst, as illustrated in Figure 2, by using chemical vapor deposition (CVD), electric arc discharge and laser ablation methods [11, 12].

Mechanical durability of CNTs, which achieve high tensile strength, becomes an important nanomaterial for biological applications required long-term functionality [13]. Although it is chemically inert, it can be made functionalized with various polymer or biomolecules in order to be used in different applications like improvement in cell bioactivity studies [14].

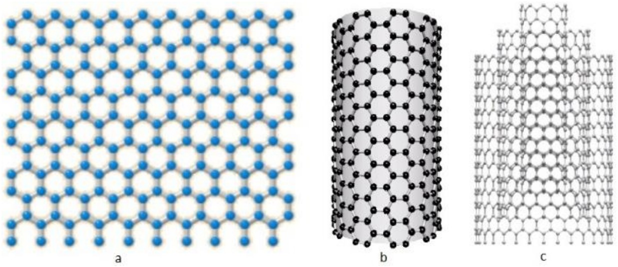

Figure 3. Carbon nanotube structures. (a) graphene sheet, (b) SWCNT, (c) MWCNT [35]

Carbon nano-fibers (CNFs) are consisted of overlapping multi-walled graphene structures, thus there is an important similarity between CNFs and MWCNTs [15]. In a study carried out, vertically aligned CNFs (VACNFs) is produced by means of catalyst on substrate and is covered with polymer polypyrrole (PPy) for keeping them independent, it was reported that as a result of these steps, better interaction and adhesion with cells is obtained [16]. While longer growth is provided with thinner and less conducting films in neuritis and cell growth fields, it is reported that broader growth is provided with thicker and conducting films [17].

These studies showed that factors such as conductivity, surface, and thickness affect nerve cell morphology. Various studies on what effect is produced on the cells using different CNTs and modifications show that SWCNTs, MWCNTs, and CNFs can be used as a base material for nerve cells [18-20].

III. THE USE OF CNTS AT ELECTRODE TISSUE INTERFACE

CNTs offer important advantage thanks to its unique mechanical and electrical properties at the interface contacting with tissue in neural implants. Neural electrodes being at the interface between living tissue and electronics should adapt to mechanical and bioactivity differences. It meets many requirements affecting the neural interaction with superior electrical and mechanical properties. Researches generally focused on growth and branching of nerve cells, electrical interfacing with neurons and developments of neural prosthesis fields.

Factors being effective on stimulation electrodes used in neuro-prosthetics applications for maintaining its performance for long term are distance between cells and stimulation electrode arrays and reactions occurred at interface. Since flat electrodes having smooth surface cannot penetrate into dead or aged cell layer on cell surface called as glia layer, stimulation threshold may be higher and SNR in recording may be lower. It is mentioned that number of electrodes should be increased for increasing the resolution in visual prosthesis applications.

Reduction in electrode size for increasing the electrode number leads to increase in impedance, thus using electrodes penetrating into 3-D tissue and having larger effective surface area in the same geometric area is required. In this point, micro based electrode arrays produced with CNTs may meet the expectations, because CNTs has high aspect-ratio rate. On the other hand, since stimulation electrode arrays would perform both recording and stimulation, electrode site should be determined in the optimum way for both of them, such that when electrode size becomes too small, stimulation current threshold decreases, but SNR decreases significantly with the increasing impedance.

Reactions at electrode tissue interface may be capacitive or faradaic. A simple electrical circuit that includes a capacitor and a resistor in parallel, as shown in Figure 4 can model these reactions. As the capacitance increases, the impedance decreases, which result in low noise level and wider safe electrical stimulation window. While faradaic reactions contain oxidation-reduction reactions, capacitive reactions represent current change with charge and discharge at electrode electrolyte interface and have an important place in electrode design [21, 22].

Capacitive nature of CNTs provides another important advantage in visual prosthesis applications. Recording and stimulating from many different points of targeted area provide high resolution for neural applications, which creates concept of multi electrode array (MEA). Devices engineered with this concept include a substrate, middle layers, and different size or diameter microelectrodes. This device is connected to an external circuit and stimulates neural tissue or record neural activity.

Electrode is a unit, which is the nearest part of the system to the live tissue and only touches to the tissue. It is needed that electrode-tissue interface provides some different aspects, such as biocompatibility, stimulation mechanism and mechanical durability, for biologically adaptation with cells and electrically efficiency.

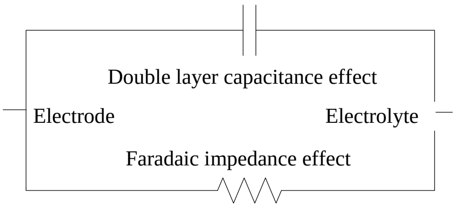

Figure 4. Circuit schematic of electrode-tissue interface

Electrical stimulation initiates with the depolarization of the membranes of cells, which are stimulated. This occurs with depolarization provided with ionic current flow between at least two electrodes, which are close to the cells. Biphasic and monophasic waveforms are used in many applications. Current pulses are defined with charge delivered, charge density, current amplitude, current density, and pulse frequency. Charge-balanced typical current waveform and its parameters are given in Figure 5.

Current controlled biphasic waveforms include cathodal and anodal phases which have equal charge, thus it is certain that waveform is charge-balanced [20]. Charge required for stimulating the cell is calculated with current and pulse duration. Current depends on pulse duration. When short pulse durations are used, currents become higher. Strength-duration curves obtained by using various durations are different.

Slope of these curves was similarly seen in species like monkey, pig, and rat. This results shows that threshold-duration relation is not much dependent on species. While a strength-duration curve is characterized by a time constant and asymptote, rheobase is asymptote of the fit curve, and chronaxie are used as duration when threshold is two times more rheobase [35].

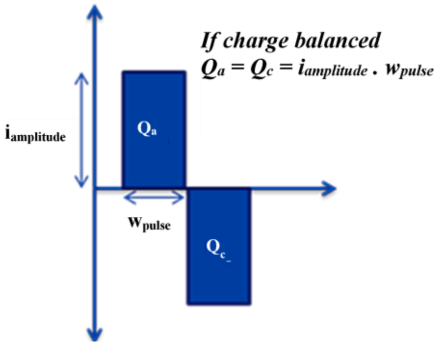

Figure 5. Biphasic waveform with cathodal and anodal phases

Neuron activity recorded as action potential shows the firing of single neuron. Recording process is performed with the microelectrodes placed being closer to the neurons whose activity is be recorded. These records taken from numerous neurons form a basis for cognitive control of prosthesis [36-38]. Classification of recording electrodes is made with impedance in 1 kHz. Techniques that can be used in-vivo and in-vitro for electrochemical characterization of neural electrodes are Cyclic Voltammetry (CV), Electrochemical Impedance Spectroscopy (EIS).

CV is performed with three-electrode structure in which potential spreads of a test electrode cyclically in the fixed rate is observed compared to a reference electrode not carrying current. EIS includes the measurement of electrical impedance using sinusoidal voltage or current in wide frequency range.

An indispensable requirement of implantable stimulation electrodes is the ability of delivering both safe and efficient current. Unsafe stimulation arises from several reasons. The former is electrochemical disintegration of stimulation electrodes and the other is neural tissue damage caused by toxic products around the stimulation electrode [36-38]. Safe electrochemical limits have been determined for various electrode materials. Even if geometric area of electrodes is used in calculations related with current and charge density, granular surface fairly increases contact area with solution, which is called as effective surface area [39].

IV. CARBON NANOTUBES IN STIMULATION ELECTRODES

Use of CNTs intended for increasing the resolution in visual prosthesis may be examined in two main titles. First of which is to use as a coating material in the metal electrode sites in stimulation electrode arrays. Results obtained from studies are reported that lower impedance, noise and higher SNR, charge injection capacity are provided with use of CNT coatings compared with the simple metal electrodes, improvement is seen in the detection of nervous activity [23-25].

Second of which is to use CNTs as an electrode material in electrode arrays from a catalyst on substrate [26-28]. The most important development on the use of CNTs in visual prosthesis applications is to develop CNT microelectrode arrays (MEAs) consisted of high-density single-walled or multi-walled CNT structures.

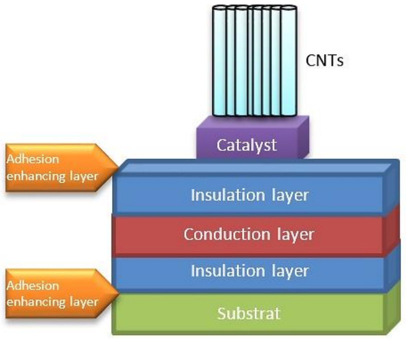

Figure 6. Layers of implantable microelectrode arrays

Respectively [24] and [23], SWCNTs and MWCNTs coatings were used with standard and indium-tin oxide MEAs. Extracellular recording of isolated retinal ganglion cells of rabbit and mice cortical cells were examined. At the end of studies conducted, improved electro-chemical properties, low impedance, high capacitance and more efficient recording and stimulation were reported. Reference [25] recommended MWCNT deposition on TiN MEAs and revealed that MWCNT-coated microelectrodes have more superior recording properties compared to normal TiN microelectrodes.

This was then tried on rat hippocampal cells. In the studies on CNT MEAs produced with high density MWCNT, it was reported that 3-D structure of CNTs provides large surface area and capacitance and impedance affects frequency dependency [27, 29]. In the studies carried out in CNT MEAs on rat retina, it was reported that SNR raises over time for recording process thanks to the improvements in tissue and electrode interface [30]. Reference [26] recommended vertically aligned MWCNT structure on quartz substrate and nanotubes were modified in order to create a hydrophilic surface providing higher load injection. [31] Compared four different electrode structures on cell cultures and ultimately reported that VACNF MEAs provides better performance in stimulation and recording compared with others.

When anatomical structure of eye and chronic experiments are considered, studies on the development of flexible microelectrode arrays for an effective interface are accelerated. At this point, CNT MEAs produced on flexible substrates rather than rigid ones attract attention. [32] Produced flexible CNT electrodes by using silicon substrate and implemented with recording of nerve cord of crayfish. It was reported by another group that CNTs were produced on flexible polyimide substrate and integrated into a chip consisting 16 amplifiers and about 10 times lower electrode impedance, about 6 times increase in capacitance and better charge injection were obtained compared with a gold electrode [33, 34].

V. CONCLUSIONS

Dealing with the reasons encountered in common materials at electrode tissue interface and preventing the reduction in electrode size and also restricting the increase in resolution is an important subject of neuro-prosthetics. In restorative studies for the neurological disorders using electrical stimulation, CNTs have advantageous properties allowing resolution to be increased such as adhesion of CNTs surface to cells, chemically inert structure, high electrical conductivity, being capacitive and having high aspect ratio. These properties make CNTs unique.

Since actions encountered in the metal materials at electrode tissue interface do not take place when electrode size becomes small, it is shown that it will be beneficial in increasing the resolution, which is one of the challenges required to be overcame in visual prosthesis field. It is obvious that flexible CNT MEAs are promising in neuroscience.

However, understanding the interaction between CNTs and living tissues is a condition for developing safe, efficient, and durable implants in order to be used for long time. Therefore conducting detailed clinical experiments on animals on biocompatibility, electrode corrosion, toxic effects, durability under long-term stimulation and recording is of importance for revealing whole potential of CNTs.

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