Microelectrode Arrays: Architecture, Challenges and Engineering Solutions

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Abstract Neural interfaces are connections linking the neuronal systems with electro-mechanical systems for information exchange. Microelectrodes of various designs have been fabricated utilizing both metallic and non-metallic materials so that they can be employed as neural interfaces. Recent studies have shown that the performance of microelectrodes can be enhanced significantly through structure controlling, surface chemistry and biotechnology. This review highlights the challenges including invasiveness, stability and selectivity associated with the employment of common electrodes as interfaces for neural recording and stimulation. It also includes controlling of electrode material and geometry as engineering solutions for the aforementioned challenges. Due to their high surface area, small size and high electrochemical properties, nanostructured electrodes show promise as electrodes that could be employed as neural interfaces for stable signal recording and stimulation. We hope this work will provide a concise picture of the evolution and the progress of current neural interfaces technology, the development of which is still in progress.

Keywords Microelectrode arrays · Neural interfaces · Microelectrodes architecture

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1 Introduction

As neurons in the nervous system communicate by electrical signals, neuroscience has given great attention to understanding how they are electrically connected in their networks as a major key to exploring the physiological and pathological functions of neurons [1]. Neural interface is an effective tool that enables the information to be exchanged in two directions within the nervous system. Electrical stimulation is a process by which the introduced information to the nervous system can be employed as an external control. The contraction of muscle resulting in stimulation of motor nerves is an example of external control [2]. Recently, brain–machine interfaces have been used to control prosthetic limbs by enabling users to supervise and process the activities of neurons. Deep brain stimulation is an effective method to treat patients suffering from Parkinson's disease [3], mental illness [4], depression [5], obsessive compulsive disorder [6] and epilepsy as neurological disorders by applying pulses of voltage or current to particular profound regions in the brain. Furthermore, electronic devices have been successfully instilled in the brain, eyes and cochlea to elicit and iterate the missing or weakened sensory and muscle function. In such devices, neural interfaces are the most important components [7, 8]. To measure the action potential and record the neural activity, different methods have been applied. These methods include: (a) extracellular recording and stimulation, (b) intracellular recording and stimulation, (c) technologies of optical imaging and stimulation and (d) methods designed to record signals of in extensive neural populations such as electroencephalography, magnetoencephalography and functional magnetic resonance imaging and electrocardiography.

Intracellular and extracellular recording are two prime electrophysiology methods that have been employed for measuring action potential and realization of neural information processing in neural circuits. Intracellular recording is more suitable for sensitive recording, but it needs rending a part of plasma membrane to approach the cell abdomen directly. Therefore, intracellular recording is a highly invasive method and difficult to perform causing significant limitations for long-term or large-scale recording. Extracellular recording, however, is a non-invasive method and supports long-term recording, but the weakness in signal strength and poor quality of the recorded signals are significant limitations of this method [1, 8]. For recording of action potential, microelectrodes should be close to neurological target cells, the surface area of the electrode should not exceed 4000 μ^2 for single unit recording and the ratio of signal to noise of the recorded action potential should not be less than 5:1. Electrochemical impedance is one of the most important electrochemical properties of the recording electrode. Signal-to-noise ratio has an inverse relationship with the electrode impedance, as lower impedance is equivalent to having higher signal-to-noise ratio. Furthermore, amalgamation of high impedance of the electrode and the distribution of the capacitance between the recording amplifier and the electrode leads to reduction of high frequency response of the electrode [9].

Many materials such as platinum, gold, stainless steel, tungsten, iridium oxide and titanium nitride have been used to fabricate the recording electrodes [10]. Neural interfaces need to be implanted deeply in the brain to record the action potentials of neurons; therefore, the implantation process will be accompanied by significant clinical risks represented by tissue damage and infection of target sites. For less tissue damage and accurate long-term recording, implanted interfaces with smallest cross section and largest number of electrode sites are the ideal interfaces. Microelectrodes are used to stimulate neurons as well as signal recording. Current picoamperes range is required to excite single neurons by the technique of patch clamp while current in the microamperes and milliamps ranges are required for nerve and muscle stimulation respectively. Microelectrode arrays are the most important component in the brain–machine interfaces as they act in a way that facilitates direct contact between the neural tissue and the electrical sensor. To obtain harmonious signals recorded from small clusters of neurons with retention of micro-stimulation abilities, microelectrode arrays are fabricated in a way that enables them to provide a low impedance path for the charge movement represented by charge injection and charge transformation. For low impedance, microelectrode arrays were made of highly conductive materials and fabricated in specific geometries [11]. To decrease the impedance of the microelectrode and improve the neural recording, porous structures such as carbon nanotubes, Pt-black and high-conductive polymers were employed to increase the effective surface area of the exposed part of the electrode [12–15].

The use of electrical stimulation of neural tissue goes back to the time of the invention of electricity. Electrical shock with 400 V from catfish was used for pain relief and as a treatment of several diseases by Ancient Egyptians in 2500 BC [16]. Also, there is historical evidence that refers to the use of electricity in religious rituals as a means to influence the spirit [17]. For pain relief and stimulation of blood circulation, ancient Greeks employed electric eels to apply electrical pulses in foot baths. Benjamin Franklin [18, 19], in 1759 looked into the contraction of muscles as a result of an electrical shock. A fuzzy concept was introduced in 1791 by Luigi Galvani illustrating the electricity in an animal's body after electrically stimulating frogs legs [20]. In the year 1939, a major development in the design of neural interface occurred when Hodgkin and Huxley [21] studied the electrical signals recorded from single neural fibre by reduction of neural interface size. In 1960, an important attempt in use of the neural interface system was done by Evarts [22] when electrophysiological experiments were conducted on the primary motor cortex of springy monkeys. Evarts pointed out that the firing rate of solitary neurons highly corresponded with the force created by the joints of the moving arm. Another significant transitional step in neural interface design and application took place in 1985, when microwire array electrodes came into force when dealing with a large number of patients [23, 24].

Electrodes made of diverse materials with different shapes and geometries have been employed as interfaces for neural recording and stimulation. These electrodes can be classified into two main groups: metal-based electrodes and non-metal-based electrodes.

2 Metal-Based Electrodes

Metals of high electrochemical properties and good biocompatibility have been used to fabricate electrodes for neural interfaces. These electrodes have been designed in different geometries to match the biological and electrochemical requirements.

2.1 Microwire Arrays

Microwires were the first electrodes made of sharpened metal and were used to record electrical signals chronically from the individual neuron in the brain by implanting the electrodes inside the brain. The wires were totally insulated except their tips, which were left uninsulated to inject neurons with current pulses and record their extracellular potentials [25].

Figure 1 is an exemplary array of microwires. Nontoxic metals of high corrosion resistance such as gold, platinum, tungsten and stainless steel were used to fabricate microwire arrays [26]. Stainless steel microwires, with a diameter of 80 μm, were used to record the action potentials from stimulated neurons of animals that had been awake for more than week [27]. As a sharpened steel microwire electrode has insufficient rigidity, Hubel [28] used pencil-like tungsten microwire electrodes with a tip point of 0.5 μm diameter for recording signals receipted from mammalian nerves. The electrodes were insulated with a suitable varnish up to the tip. The measurements showed that tungsten microwire electrodes have a low signal-to-noise ratio and slow signals were lost when a high-pass filter was used to diminish the noise. To increase rigidity, elasticity and corrosion resistance of

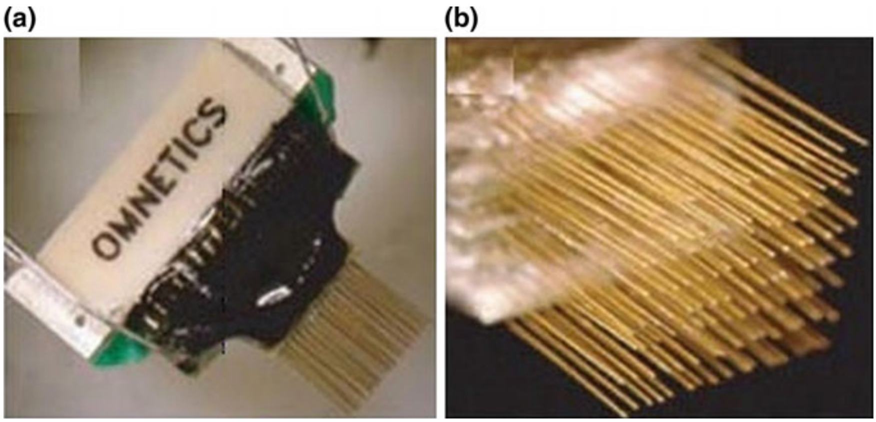

Fig. 1 Microwire arrays. **a** Arrays of microwires connected to the connector, **b** dense arrays of microwires [25]

microwire electrodes, iridium microwires were employed as microelectrodes for measurement of action potentials. It was reported that iridium has higher rigidity, corrosion resistance and elasticity than tungsten. Furthermore, increases in maximum charge density can be attained because it is possible to activate iridium surfaces electrochemically [26]. It was shown that an implemented array could consist of from 4 to over 100 wires. Nicolelis et al. used 704 microwires in 10 arrays to record 274 neurons individually in monkey cortex [29, 30]. An extracellular recording with spike amplitude of 60 μV was achieved by microwire tetrode from individual pyramidal cells distributed within a radius of 50 μm [31]. The ease of fabrication is an obvious advantage of microwire electrodes [32]. Another advantage of microwire electrodes is that these electrodes can access deeply in the brain to reach the target neurons [33]. The main obstacle of the microwires technique is that the bending of microelectrodes during implantation leads to loss of accuracy of the positions of the wire tips relative to each other [26].

2.2 Planar-Type Microelectrode Array

Planar-type microelectrodes made of nontoxic and high corrosion resistance metals such as gold, platinum, iridium and titanium nitride are a common electrode with a diameter of a few tens of micrometres. Planar microelectrodes are a cell culture dish used to study the activity and plasticity of the neural network [15]. To facilitate the observation of the cultured cells using conventional transmitted light microscopy, leads of one of the aforementioned metals are usually embedded in a glass wafer substrate. Figure 2 shows the planar-type electrode. It is usual to coat the glass substrate with laminin or polylysine to promote the cell adhesion and increase the sealing resistance between the substrate and the cultured cells. The substrate consists of 1–100 electrode sites spaced at inter distances of 100 μm. Organic or inorganic materials such as epoxy resin, polyimide, silicon oxide and silicon nitride

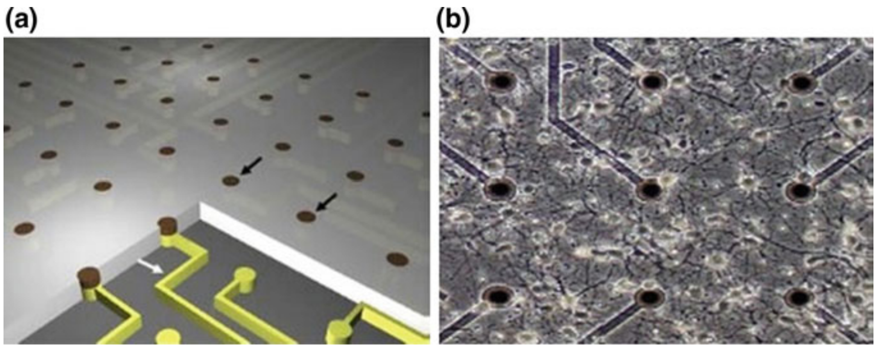

Fig. 2 **a** Planar-type electrode connected to contactor lines, **b** hippocampal neurons are cultured on the planar-type electrode [15]

are used to insulate the electrodes from each other. All electrodes are connected with a contact pad by thin contactors to transfer the captured signals to the amplifier [34]. It was reported that the impedance of a standard gold electrode with a diameter of 60 μm in electrolyte solution is 50 kΩ at 1 kHz. Individual sensing pads must be made smaller to match the size of the individual neurons. However, reduction of the surface area that accompanies the reduction of the sensing pad size results in a significant increase in the impedance and consequently decreases the signal-to-noise ratio. Nanostructures such as gold nanoflakes, gold nanopillers, carbon nanotubes or Ti_3N_4 compensate for the lack in the surface area resulting from the reduction of the electrode size [35].

2.3 Mushroom-Shaped Microelectrode

Although, micro patterned electrodes afford non-invasive and long-term extracellular recording, they suffer significantly in signal strength and quality. Recording understrength and quality signals restricts microelectrodes from sensitive recording such as, disinhibition, synaptic integration and under threshold oscillations [35].

To enable microelectrodes for such applications, Spira et al. used a micro-size protrusion made of gold with a mushroom shape as a sensing electrode (Fig. 3a). By increasing the electrical coupling coefficient between the neuron and the microelectrode to 50% recorded by a gold mushroom-shaped sensing electrode compared to 0.1% for the gold planar microelectrode array, it becomes possible to record synaptic potentials in addition to the action potentials. The enhancement in cell recording achieved by using gold mushroom-shaped electrodes was attributed to three main causes. The first is that the unique geometry of the electrode enables neurons to engulf the electrode as shown in Fig. 3b. The second is the high seal resistance between the cell membrane and the mushroom-shaped electrode and the third is because of the increase in the junctional membrane conductance [1].

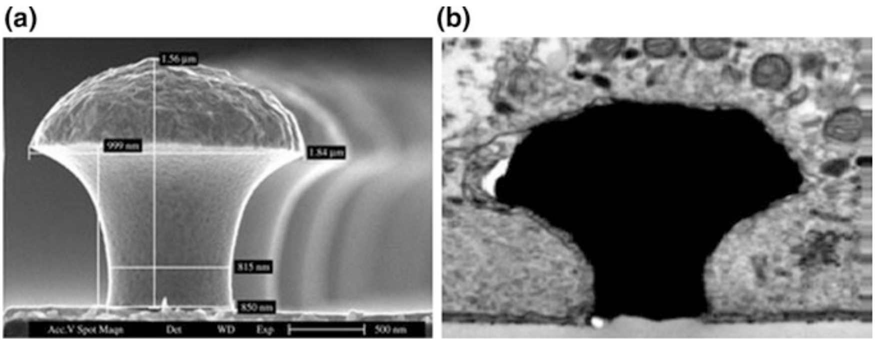

Fig. 3 **a** SEM image of gold mushroom-shaped microelectrode, **b** TEM image shows the Aplysia neurons engulf the mushroom-shaped electrode [1]

2.4 Nanostructured Microelectrodes

Great efforts have been exerted to overcome challenges such as inflammation and noise associated with the use of neural interfaces for neural stimulation and signal recording. Previous studies showed that the mechanical, physical and chemical properties have a crucial influence on the performance of the neural interfaces [36]. Ordinary interfaces in brain–machine interfaces utilize a small number of large electrodes for signal recording. It was reported that electrodes with diameter range of 10–100 microns were used in brain–machine interfaces for signal recording while electrodes with size of 4–8 mm were used for deep brain stimulation [37, 38]. As the human brain contains approximately a hundred billion neurons and each neuron has a diameter of about 10 microns, accurate monitoring and precise control on the neural circuit activities requires electrode arrays of high density and small size [39]. The efficiency of neural electrodes for neural signal recording and stimulation is greatly affected by the electrical coupling and the contact between the cell and the electrode surface, the electrochemical properties of the electrode and the biocompatibility of the material at the contact sites [11].

2.4.1 Nanowire Arrays

Due to their high aspect ratio, nanowires made of nontoxic and high corrosion resistance metals have attracted a lot of attention in different applications. Employing nanowires as neural interfaces is one of their important applications [40]. Platinum nanowires with a diameter of 150 nm and height of 1.5 µm were deposited on planer platinum electrodes by means of focused ion beams (Fig. 4a). A layer of Si_3N_4/SiO_2 with a thickness of 350 nm was deposited by plasma-enhanced chemical vapour deposition to insulate the substrate. Platinum nanowires were utilized to stimulate and record electrical signals from mitotic cardiac cells [40]. Bruggermann et al. [41] have fabricated gold nanowires with a

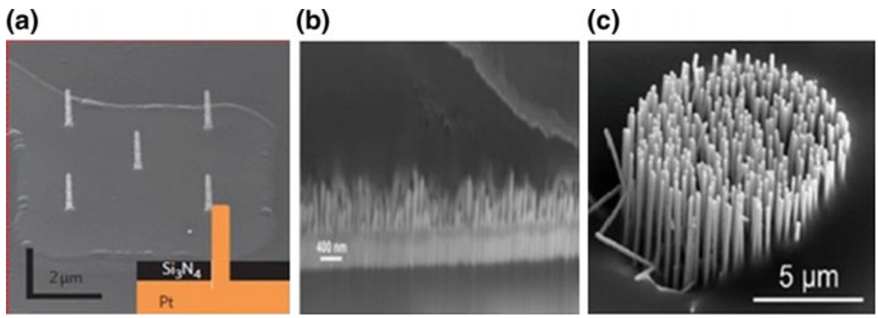

Fig. 4 SEM images of metal-based nanowire electrodes. **a** Platinum nanowire electrode [40]. **b** Gold nanowire electrode [41]. **c** gallium phosphide nanowire electrode [43]

diameter of 60 nm and height of 300–400 nm on pads with diameter of 2 μm (Fig. 4b). Extracellular potential recordings were taken from cardiac muscle cells (HL-1) using the gold nanowire electrode. The maximum-recorded amplitudes achieved by gold nanowire electrodes were 100% higher than those achieved by planar gold electrodes [42]. Gallium phosphide nanowires with 70 nm diameter and 5 μm length were fabricated by Suyatin et al. [43] on substrate of 12 μm diameter with a pitch size of 500 nm. A gold film was subsequently deposited on the top of the nanowires. Gallium phosphide nanowire electrodes are illustrated in Fig. 4c. Gallium phosphide nanowire based electrodes were employed to perform acute recordings in the rat cerebral cortex.

2.4.2 Nanotube Arrays

Previous studies have shown that vertical electrodes are able to achieve intracellular recording of action potential with high signal to noise ratio. These studies pointed out that the geometry of vertical electrodes has a crucial influence on the sensitivity and quality of recorded signals. Nanotube geometry was pointed out as an important factor influencing the performance of the vertical electrodes as the cell membrane wraps around and extends into the nanotube, thus the gap between the electrode and the membrane is significantly reduced [44–46].

Recently, Eick et al. [47] developed a new nanoelectrode consisting of iridium oxide nanotubes (Fig. 5a). After cardiomyocytes were cultured on the fabricated nanotube electrode, the images of scanning electron microscopy showed that the cell membrane wraps around and extends into the pore centres. Electrochemical measurements showed that iridium oxide nanotube electrodes possess lower electrochemical impedance and higher capacity of charge storage compared to gold nanopillar electrodes having the same surface area. The author demonstrated that the geometry of nanotubes promotes cell–electrode coupling and larger signals can be recorded compared with solid electrodes. Moreover, stable recording can be achieved by nanotube electrodes as they provide non-invasive and have longer

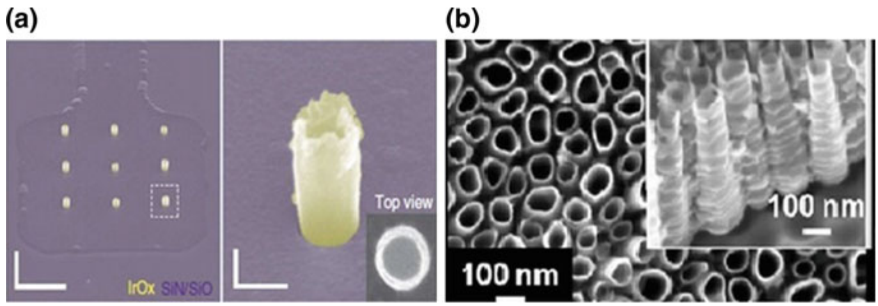

Fig. 5 **a** Iridium oxide nanotubes array on a platinum substrate (*left*). Iridium oxide nanotube (*right*) [47]. **b** TiO_2 nanotube array [48]

intracellular access. As a result, the author pointed out that nanotube geometry significantly enhances nanoelectrode performance.

In many studies, titania nanotubes were identified as a promising form of biological electrode as they possess high corrosion resistance, distinctive mechanical properties, elevated specific surface area in addition to excellent biocompatibility [44, 45, 48]. TiO_2 nanotube arrays are illustrated in Fig. 5b. It has been established that a titania tubular structure has a great potency for application in the medical area. Results have shown that TiO_2 nanotubes enhance the mineralization, proliferation and adhesion of osteoblasts and expedite the recovering of bone tissue. It has also been established that tube dimensions have a crucial influence in the differentiation of mesenchymal stem cell [44]. It was suggested that tube pores and the spacing in a titania tubular structure offer a substantial pathway for continuous supply of ions, nutrients and proteins required for healthy cell growth [45]. The anatase phase shows a better support for formation and growth of hydroxyapatite than rutile [46]. Park et al. showed that tube diameter has an important effect on adhesion as well as proliferation of mesenchymal stem cells. Authors have pointed out that tubes with a diameter of 15 nm improve the cell activity when the spacing between nanotubes is less than 30 nm while cells showed programmed death when they were cultured on tubes with a diameter larger than 50 nm [46]. Tube morphology has a critical effect on the electrical behaviour of a titania tubular structure. Tubes with wall thickness of 30–40 nm showed low impedance. Sun et al. attributed the electrical behaviour of these nanotubes to the thickness of their walls being sufficient to that being required for charge transformation [49].

Many approaches have been employed to fabricate TiO_2 nanotubes. These approaches include templating, sol-gel, photo-electrochemical etching and anodic oxidation. Low cost and the possibility of fabrication of TiO_2 nanotubes in a wide range of morphologies, anodic oxidation is generally used to fabricate titania tubular structures. Anodization parameters such as applied voltage, electrolyte type, electrolyte pH and anodization time have significant influence on the fabricated nanotube morphology [50]. Figure 6 shows TiO_2 nanotube arrays with different morphologies fabricated by controlling the anodization voltage. It was shown that subjecting the nanotubes to the annealing process at 450 °C enhances their

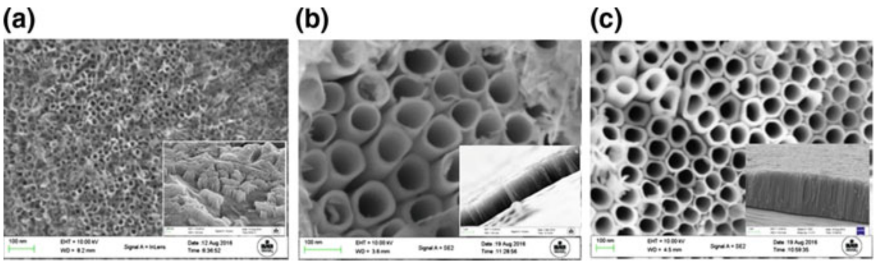

Fig. 6 TiO_2 nanotube arrays fabricated in ethylene glycol containing 0.5 wt% NH_4F and 4 vol.% of deionized water at anodization voltages of **a** 10 V, **b** 40 V and **c** 60 V

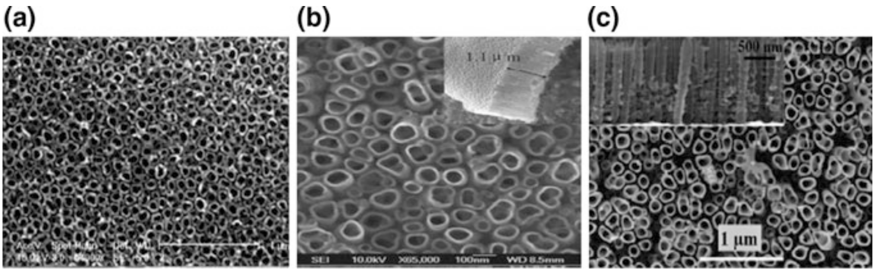

Fig. 7 TiO_2 arrays doped with **a** carbon [56], **b** nitrogen [55] and **c** tin [57]

electrochemical properties as a result of successful transformation from amorphous to anatase crystal structure [51]. As titania nanotubes inherently possesses low conductivity, which is highly desirable for neural interfacing, therefore electrochemical and physical methods have been employed to introduce metallic and non-metallic electrically active particles such as Pt, Ag, N and C into the titania lattice to enhance the electrical properties and biocompatibility of titania nanotubes [52–54]. It was reported that doping with nitrogen improved the electrochemical properties represented by electrochemical impedance and charge storage capacity [55]. To improve the capacitive properties of TiO_2 nanotubes, Zhang et al. have fabricated carbon-doped nanotubes. The authors show that the presence of carbon atoms in titania tubular structure improve the capacitance of the nanotube layer [56]. Kyeremateng et al. have investigated the effect of Sn doping on the electrochemical properties of TiO_2 nanotubes. The authors showed that Sn-doped nanotubes have higher capacitance than simple nanotube arrays [57]. Figure 7 illustrates TiO_2 nanotube arrays doped with different elements.

3 Non-metal-Based Electrodes

Due to the wide range of their structure, non-metals with their various physical, chemical and mechanical properties have been employed in different applications. One of their important applications is the neural interfaces. Neural electrodes made of non-metals have been utilized to overcome the limitations related to the use of metallic electrodes including inflammation, tissue damage and low flexibility.

3.1 Silicon-Based Electrodes

The emergence of technologies such as lithography techniques by which complicated structures can be fabricated has been followed by micromachined electrodes used to stimulate neurons and record potential signals [11, 58–60]. To overcome the

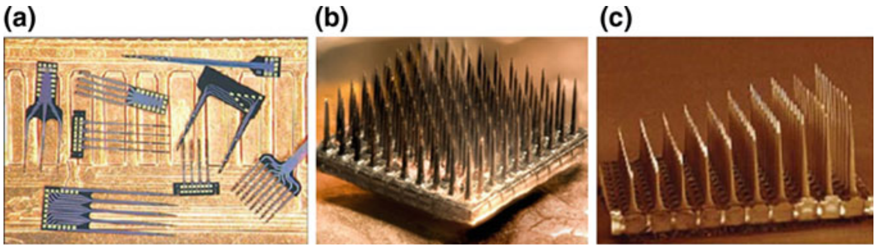

Fig. 8 Micromachined electrodes **a** different types of Michigan electrodes [62]. **b** Utah electrode (*flat array*) [63]. **c** Utah electrode (*incline array*) [63]

difficulties associated with the curvature of the wires used with the microwire technique, micromachining techniques utilizing silicon arrays have been used to generate a more rigid structure. As silicon arrays are smaller in size than that of microwire electrodes, larger number of sites in different layers of the cortex can be recorded by silicon arrays for the same quantity of tissue displacement [61]. There are two major models of micromachined electrode. The first model was fabricated in the University of Michigan and consists of a shank with silicon substrate having several electrode sites. Different types of Michigan electrodes are illustrated in Fig. 8a. The Utah array is the second model of micro machined electrodes. In Utah array, sharpened needles made of silicon with lengths up to 1.5 mm and diameter ranging from 1 to 100 μm were electrically insulated up to their tips using polymers with a good biocompatibility like parylene-C or polyimide. The bare tips of the silicon needles were coated with a conductive metal such as platinum or iridium. The architecture of Utah array provides the ability of signal recording from the individual neurons with high locative resolution as well as stimulation of the target neurons. Due to their biocompatibility, geometry and architecture, Utah arrays can be deeply inserted into the brain safely. Therefore, Utah arrays are widely used in neuroscience and medical researches [11, 62]. Figure 8b and c shows flat and inclined microelectrode arrays.

3.2 *Polymer-Based Electrodes*

Materials of rigid structures are usually used in conventional electrodes. Using stiff electrodes cannot provide vigorous interfaces with neurons and precludes long-term signal recording. The poor contact between the stiff interfaces and the soft neural tissue causes aggressive contact at the tissue-interface contact sites which leads to tissue damage and inflammation [63]. To avoid neural damage and inflammation of the implant sites, flexible arrays made of polymer-based electrodes have been developed to provide less invasive methods for neural stimulation and signal recording. Polymers such as polyimide, parylene-C, liquid crystal polymer, SU-8, benzocyclobutene and silk are common polymers used in fabrication of flexible

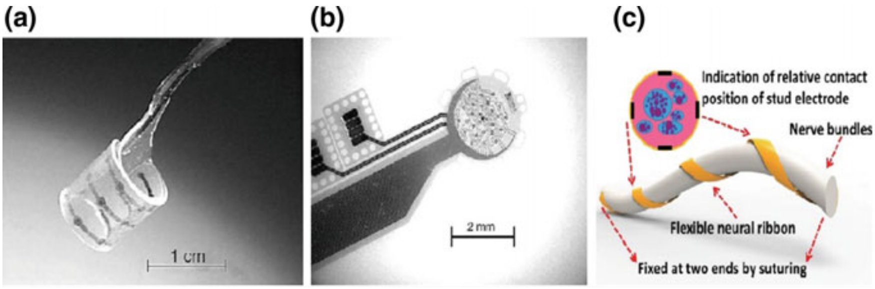

Fig. 9 Different types of flexible electrode. **a** Cuff electrode with polyimide substrate [74]. **b** Sieve electrode [74]. **c** Flexible ribbon electrode [76]

arrays [64–69]. Because of their good mechanical flexibility, high corrosion resistance and good biocompatibility, flexible arrays are widely used for long-term neural recording [70]. The variety of flexible electrode design was illustrated in Fig. 9. The low elastic modulus of polyimide and parylene-C electrodes (3.2 GPa) enable them to lessen the tissue damage and afford longer term recording than that of silicon [69–71]. In 1970s, Hoffer and Loeb successfully recorded neural signals by implanting cuff electrode and flexible platinum wire in the lumbar spine of a cat [36, 72]. The next attempt for flexible interfaces was made by Donaldson et al. to improve the flexibility and electrical conductivity by using the cuff interface with silicone rubber [35, 73]. As Parylene base electrodes have high flexibility, they show extremely consistent coverage of the tissue surface and this enables them to provide steady electrical contact and subsequently high signal to noise ratio [38].

A parylene-based microelectrode array has been employed for neural recording and drug delivery by utilizing electrode sites at different sides include the top, back and edges. Cuff electrodes made of hybrid polyimide entrenched in silicon guidance were fabricated to stimulate the peripheral nerves and record sensory signals. It was noticed that nerve trunks wrap around the cuff electrodes and furthermore, the muscles can be activated by stimulation of the motor fibres [74, 75]. However, although polymer electrodes are common neural interfaces, there are two main limitations for the use of these electrodes. The first is the difficulty of signal recording from neurons with different diameters and the second is the inability of communication with very small nerves (less than 300 μm in diameter). As a nerve size has a random distribution in the body, the predefined polymer electrodes lose the perfect match with target nerves [76, 77].

3.3 Nanostructured Electrodes

For many reasons nanomaterials are a promising technology in neural interfacing fabrication. Neurons are electroactive cells and the electrochemical properties of improved nanostructure can meet the requirements of the charge transformation. The distinctive chemical and mechanical properties of nanoscale structures strongly support the neural tissue for a long-term implantation. Furthermore, the high biocompatibility of improved nanomaterials solves the biological problems related to the implanted interfaces [78]. The discovery of nanomaterials with their unique properties of high electrical conductivity, exceptional chemical stability, excellent mechanical properties and high surface area moved neural interfaces to a new stage by enhancing the sensitivity and selectivity in addition of improving the biocompatibility and the response time [79].

3.3.1 Nanowire Arrays

Non-metallic nanowire used to record the electrical signals from the biological systems show higher sensitivity in observation of the changes in action potentials for cultured neurons than micro-size electrodes [80]. Nano wires made of semiconductor materials are a powerful technique and have a great impact on a wide range of scientific areas such as electronics, photonics, bioscience and healthcare. The good understanding of nanowire growth mechanism enables the production of nanowires with a homogeneous composition and diameter and, as a result, electrical and optical properties can be highly controlled. The correspondence in nanosize between the nanowires and the nano components in biological systems makes nanowires a promising candidate as a sensitive tool for investigation of biological systems [81]. As the bend of nanowires enables them to protrude between the lineaments of the cellular membrane, nanowires have a tight connection with the neural membrane. Decreasing the gap between the electrode surface and the cellular membrane enhances signal-to-noise ratio and increases the sensitivity of signal recording [82]. Two major techniques Langmuir–Blodgett and dry transfer techniques have been used to grow nanowire arrays on surfaces of silicone/silicone oxide substrate [83, 84].

Different strategies have been used to fabricate silicon-based vertical nanowires. Duan et al. [85] employed electron beam lithography to create gold islands on the gate of a nanowire field-effect transistor with nanoscale to use them as precursors for germanium nanowire growth by vapour–liquid–solid mechanism. By using the atomic layer deposition technique, germanium cores were coated with SiO_2 and subsequently etched by hydrogen peroxide and the result was vertical glass tubes (Fig. 10a). The author showed that these glass tubes have been successfully used for intracellular potential recording by penetrating plasma membranes of cardiomyocyte cells. To improve penetration, fabricated nanotubes were coated with phospholipid which makes it difficult to culture cells on these nanoelectrodes. Therefore, cells were cultured on separated substrate. As it is shown in Fig. 10 b, Robinson et al. [86] have fabricated silicon nanowire, using plasma etching techniques, which were insulated by thermally grown SiO_2 film. The silicon oxide film was removed from the tips of silicon nanowires followed by coating uncovered tips with vapourized platinum or gold film. The fabricated silicon nanowires were

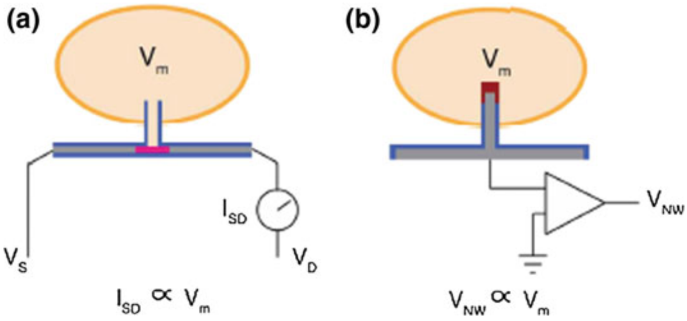

Fig. 10 Two strategies to fabricate nanowire electrode [8]. **a** Silicon nanotube on an insulated germanium nanowire. **b** Silicon nanowire with gold or platinum coated tip [8]

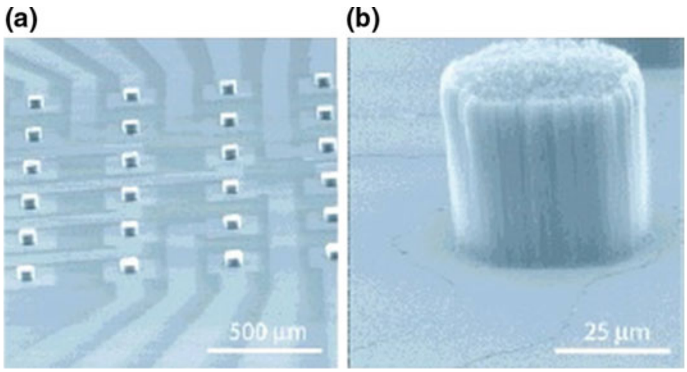

Fig. 11 SEM images of **a** Carbon nanotube electrode array [94]. **b** Carbon nanotubes electrode [94]

employed to stimulate individual neurons as well as record neural action potential. The main obstacle of the nanowire interfacing technique is the inherent high electrode impedance. It is worth mentioning that although a single pad in the interface contains a number of nanowires, the impedance of the electrodes is still too high to make it possible to record subthreshold potentials [40, 86]. Theoretically, increasing the number of the nanowires in a single pad may solve the problem of high impedance of electrodes. Nevertheless, high density of the nanowire electrodes precludes electrode to cell interior in intracellular recording.

3.3.2 Carbon Nanotube Arrays

Carbon nanotubes based electrodes are one of the most common nanotube electrodes because of their distinctive properties including very good electrical conductivity, high tensile strength, superior thermal conductivity and high aspect ratio [87–91]. Figure 11 shows an image of a carbon nanotube electrode array (a) and carbon nanotube electrode (b). Carbon nanotubes have been utilized in neuroscience research with one important application in recording of electrical activities of neurons [92, 93]. It was illustrated that carbon nanotubes enhance cell attachment and promote differentiation and growth of neurons [61]. Wang et al. [94] showed that vertically aligned carbon nanotubes offer a high level of charge injection (1–1.6 m C/cm^2). The authors demonstrated that carbon nanotubes increase the active surface area and decrease the impedance of the electrode–tissue interface. To improve the performance of single wall carbon nanotubes interface and achieve long-term recording, the nanotubes were electrochemically co-deposited with polypyrole. The modified electrode showed high injection level, good stability and low impedance [95].

4 Conclusion

In the past several decades, considerable effort has been made towards development of neural interfaces with many advantages and limitations of common interfaces being discovered. Various materials, utilizing different shapes and sizes, have been used to fabricate neural interfaces. Electrode design is important in that it has an influence on the cell–electrode coupling and tissue rehabilitation. Thin, sharp and flexible electrodes are desired for better performance in neural recording and stimulation. Lower electrochemical impedance and higher charge storage of interfaces are required to achieve good signal to noise ratio. Nanostructured electrodes are promising as their size matches the neuron size enabling signal recording for individual neurons and they can be shaped such that cells engulf the electrodes supporting enhancement of the cell–electrode coupling. As current neural interfaces have their limitations including high impedance, large size and high invasion, technology of interfaces fabrication is still in progress. This review focussed on the history and current status of neural interface technology.

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