Chapter 9
Thin Film Coatings as Electrodes in Neuroscience

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Abstract Neural electrodes are essential tools widely used in both basic neuroscience studies and clinical applications to treat various neurodegenerative diseases. In this chapter we explore the common and novel thin film materials used in fabrication of neural electrodes. Discussion will include the physical and chemical properties of thin film coating materials that make them advantageous compared to hard and solid electrodes like silicon etc. To assess the biocompatibility requirements for the neural electrodes, it is important to understand the anatomy of the brain and the neural environment. This chapter will discuss the typical immune response around the implant with coatings and the tests for biocompatibility. How nanotechnology offers huge potential in the fabrication of high performance electrodes with thin film coating are addressed in terms of the current state of the art materials and fabrication technology. At the end, the future trends in research related to thin film coatings will be presented briefly.

9.1 Introduction

Every year, thousands are disabled by neurological diseases and injury, resulting in the loss of functioning neuronal circuits and regeneration failure. Several therapies offer significant promise for the restoration of neuronal function, including the use of growth factors to prevent cell death following injury [1], stem cells to rebuild parts of the nervous system [2], and the use of functional electrical stimulation to bypass CNS lesions [3, 4]. All these different treatment options can be performed

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locally using an implantable electronic device. Though most of the ideas related to neural implants are still in fiction, a considerable amount of research effort is focused in their design and development. Current developments in this field, especially with implantable microelectrodes, have already arisen hope in opening up great opportunities for treating patients who have lost the ability to move and talk because of stroke, spinal cord injury or neuro-degenerative diseases, such as Parkinson's disease. The field has potential with possibilities to restore vision and hearing ability of people who suffer blindness or deafness due to damaged nerve functions.

Generally speaking, neural implants are designed and fabricated at the micro scale to ensure that they are as non-invasive as possible. The electrodes are designed to stimulate the neurons in the proximity of the electrodes or record the communication between neurons using safe and low electrical current. A schematic diagram of a neural electrode array is shown in Fig. 9.1. The implants also communicate with an external source such as a microphone if sounds modality is considered, which records and processes the wirelessly received inputs. Since, the dimensions of neural cells range from tens to hundreds of micrometer; it is desirable to be able to conveniently change the number and spacing of electrode sites for various applications. Micro-electrode arrays are generally created using silicon based fabrication processes. While the response from this fabrication process is positive, these electrode arrays can break during tests due to the brittle nature of silicon. The rigid electrodes often cause tissue damage, inflammatory reaction, and scar formations. Recently, polymeric materials are being studied extensively as a substrate material due to their higher flexibility and improved bio-compatibility. Handling of flexible polymer material seems to be easier during neural recordings as tested by Kim et al. [5]. With the advances in microfabrication and thin film deposition technology achieving high spatial resolution is

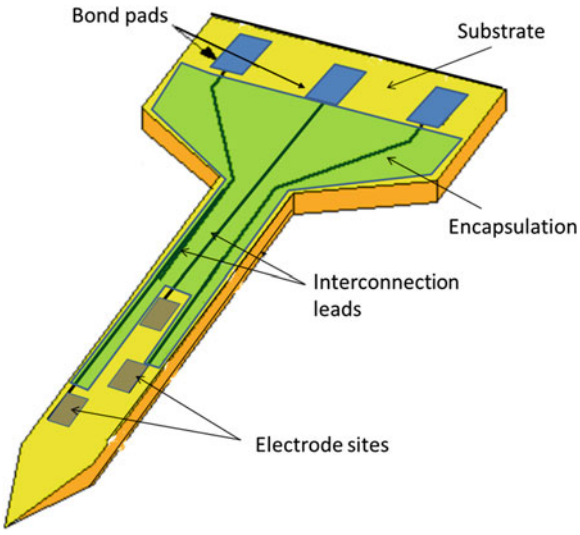

Fig. 9.1 A schematic diagram of a neural electrode array

being possible; however, achieving good electromechanical properties is a balance between the materials, geometry and fabrication techniques. Low surface area of the electrodes leads to their low charge injection capacity and high impedance. Obviously, changing the actual surface area is unpractical, so to overcome that, the effective surface area is enlarged by use of coating materials such as Titanium Nitride, Iron Oxide or PEDOT. These coatings improve the electromechanical properties but have other undesired limitations such as instability over long term use, complex deposition methods, or toxicity. As a recent progress, surface modification of the flexible metallic (e.g. platinum) electrodes by adding a thin layer of carbon nanotube (CNT), polymer nanotube or conducting polymer has shown to improve the bio-compatibility, ease of handling and use, and durability better than silicon based substrate.

Various research groups working in the field of development of neural implant devices or neuro-prosthesis have focused their work in different areas. There are a number of problems that must be studied during the development of neural implant devices. There are material issues, fabrication issues, biocompatibility issues, surgical technique issues, and so on. For example, in the 36th Annual Neural Prosthesis Workshop and the annual meeting of the National Institute of Health's (NIH) Deep Brain Stimulation (DBS) Consortium, the six plenary sessions were: Progress in Deep Brain Stimulation, Novel Interface Technologies for Stimulation, Surgical Considerations for Neural Interfaces, Chronic Recording Microelectrodes, Neural Interfaces for Sensory Information, Spinal Cord Interfaces, and Future Efforts in Neural Interfaces. If we start from the bottom up, the most important issue is the materials biocompatibility. The device must be able to perform with an appropriate host response in its intended application. Two other critical factors in the development and long-term effectiveness of all implantable devices are: spatial resolution and good electromechanical properties.

Thin film technology in general reduce the materials cost by more efficient utilization of active materials. It is also possible to tune the film properties like porosity, crystal structures and film surface roughness by controlling the deposition variables. A combination of coating and substrate materials are used depending on the overall design and application of the electrode device. Using flexible polymers as backbone structure, thin film technology made possible fabrication of implants with high charge injection properties and low impedance. Electrochemical reactions in thin film are facilitated by faster ionic transport and smaller current paths.

The present chapter is organized as follows. First, the neural environment is introduced along with various electrode materials that are compatible with the environment and thin film technology. These materials are identified and listed by reviewing recent research articles. Various physical, chemical, electrical, and mechanical properties that are required for a good electrode material are also discussed. Since the recent trend is targeted towards developing flexible electrodes due to their many advantages, the materials that have shown superior properties for substrate and encapsulation are presented next along with their relative advantages and disadvantages. Next, current state of the art coatings used on electrode

surfaces for further improvement of the electrochemical properties of stimulation and recording electrodes are discussed. The improvement of such properties is discussed with an emphasis on various surface coatings of electrodes. Then, several common techniques used in fabricating thin film electrodes and their surface modifications are briefly presented. Different methods for testing biocompatibility and bio-stability of various electrode materials are also depicted. The chapter is concluded with future trends of highly stable microelectrode and biocompatible materials for chronic neural stimulation and recording.

9.2 Neural Environment

Neurons are extraordinary among cells for various reasons. First, they are polarized, possessing receptive dendrites on one end and axons with synaptic terminals at other with high selectivity to the substrate. Second, the neuronal cell is electrically and chemically excitable. Third, nerve cells in specific zones of the brain form specific signaling networks that mediate specific behaviors. Fourth, by electrical and chemical stimulations, it is possible to accomplish physiological and anatomical changes, including pruning of preexisting connections, and even growth of new connections. All these facts are the basis of relentless research efforts in the creation of neuronal prosthesis for neuronal recovery processes (Fig. 9.2).

The astrocytes and microglia are the two major contributors in the brain's immunological reactions. These cells are very important in the study of biocompatibility and are mainly responsible for developing scar tissue around the implant or electrode sites. The development of tissue scars in a controlled process

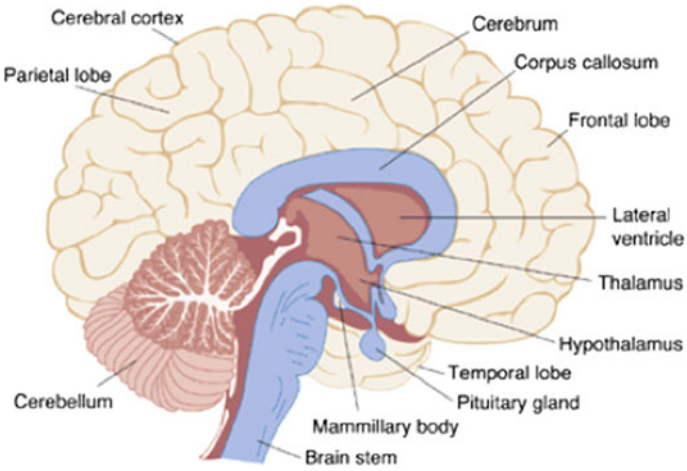

Fig. 9.2 Neural environment http://creationwiki.org/Human_brain

facilitates the implantation of the microelectrode at a fixed position in the brain. However, uncontrolled scar tissue formation may cause encapsulation of the electrode with thick tissue introducing additional impedance in the current path and eventually complete separation of the electrode from the surrounding neurons.

9.3 Requirements for Electrode Materials

Different materials such as platinum, alloys of platinum and indium, iridium, iridium oxide, titanium nitride, conductive polymers and carbon derivatives such as graphene, carbon nanotubes, etc. have been used for the fabrication of electrode arrays. Following are some properties that are important when selecting an electrode material.

- Smaller geometry for selectivity.
- Safe charge injection capability with small power consumption.
- Reversible reaction during charge injection that do not form toxic product at electrode-tissue interface.
- Low polarization and impedance at the phase boundary for efficient injection of charge.
- Long term mechanical stability and corrosion resistance for chronic stimulation applications.
- Biocompatibility of the electrode material or the coating.
- Visible to MRI, X-ray and other noninvasive diagnostic techniques.

Basically for biological application electrodes function as transducers between physiologic and electronic systems, as illustrated in Fig. 9.3.

In the neural environment, neurons communicate using bioelectric potentials that are carried in electrolytic media (cerebrospinal fluid) in the form of ionic currents via chemical species. The communication at the electrode-neuron interface or signal transduction by the electrode involves the inter-conversion of energy

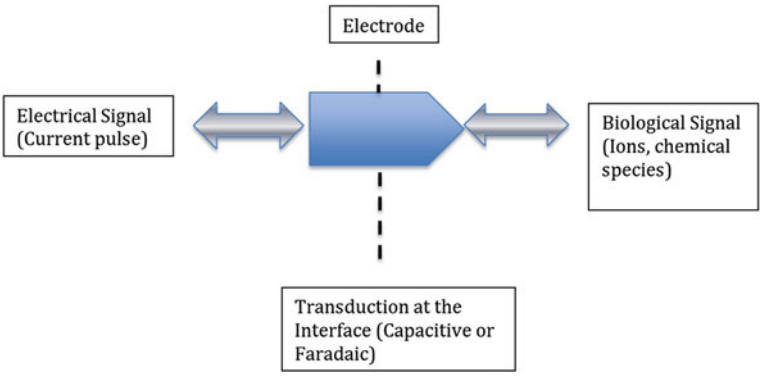

Fig. 9.3 Transduction of signals at electrode interface [101]

Table 9.1 Studies with neural stimulation device

Research group	Electrode material	Electrode geometry	Research subject
Hesse et al. [104]	Platinum	0.1 nm × 0.1^m^2	Cat retina
Humayun et al. [105–108]	Platinum	400 nm diameter disc and 25–1 25 nm wires	Human retina
Walter et al. [109]	Platinum and Titanium Nitride	100 μm (Pt.) and 50 nm (TiN) diameter	Rabbit retina
Grumet et al. [110]	Platinum	10 nm diameter disc	Rabbit retina
Rizzo et al. [111, 112]	AIROF	100 and 400 um diameter disc	Human retina
McCreery [113]	Activated Ir	GSA of 1,000 ± 200 μm^2	Cat VCN
Branner [114]	Pt	Electrode tip 0.005 mm^2	Cat sciatic nerve

that is present in the form of ionic carriers and in the form of electronic carriers (electrons and holes). This takes place by means of capacitive coupling (without net charge transfer) and or by charge transfer reactions (Faradic) in which electrons in the electrode are transferred to and from ions in the solution. The electrode–electrolyte interface is still not fully understood. Two most common models that are used to describe the electrochemical behavior are capacitive mechanism (charging and discharging of the electrode double layer, no electron transfer) and Faradaic mechanism (chemical oxidation or reduction, reversible or irreversible).

Several examples of electrodes used in electrode stimulation studies with different geometries and materials are presented in Table 9.1.

9.4 Types of Electrodes in Neuroscience

Thin film microelectrodes used in neuroscience research can be categorized in the following major types:

1. Stimulating Electrodes [6–11]
2. Recording Electrodes [10–14] (Fig. 9.4)
3. Sensing Electrodes [15, 16].

9.4.1 Stimulating Electrodes

Stimulating electrodes uses a small current pulse to initiate a functional response by depolarizing the membranes of Neurons. Depolarization is achieved by the flow of ionic current between two or more electrodes: the working electrode and the

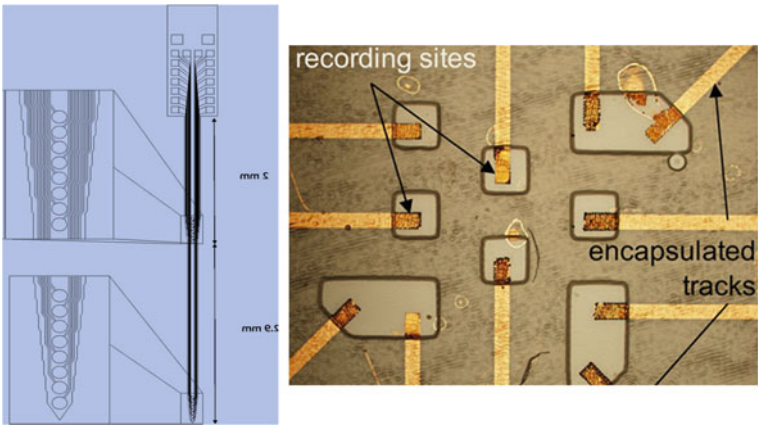

Fig. 9.4 Penetrating electrode [102] and surface electrode [103]

return electrodes. The working electrode interacts with the target cell or tissue being in its close proximity.

The stimulation used in most neural applications, is applied in a series in the form of biphasic current pulses. For the safety of the neural tissue it is very important that the current is charge-balance is to maintain the electrode potential within an optimum range. High voltage can cause irreversible reduction and oxidation reactions that may degrade the electrode and damage tissue. Other factors important to consider are pulse width and charge injection limit of the electrodes. The stimulus waveforms must be limited to current and charge densities that allow charge injection by reversible processes and at a finite rate [17].

9.4.2 Recording Electrodes

Recording electrodes are used to record signals related to neuronal activities as the input of various prosthetic device intended to treat patients with paralysis or other neurodegenerative disease [12, 14, 18]. The recording can also be used as feedback signals from the neurons that are being stimulated using stimulating electrodes like in the cases of adaptive DBS [19] and functional stimulation for epilepsy [20].

The activity of neurons is recorded as an extracellular potential, or action potential, with microelectrodes implanted in close proximity to the target neurons. For single cell recording, the microelectrodes used are very small in size with geometric surface area (GSA) in the range of 2000–4000 μm^2 or smaller. Recording electrodes are typically characterized by their impedance at 1 kHz, we will find the mention of this impedance in Table 9.2. For recording electrodes, unlike stimulating electrodes, current flow and the electrochemical changes across the electrode–electrolyte interface are not critical factors. The two most important

Table 9.2 Recent research in electrode materials

Materials type	Thin film electrode	Fabrication technique	Comments	Reference
Metal	Pt	Sputtering	Low charge injection limit, but good biocompatibility	[87, 88]
	IrOx	Electrochemical activation (AIROF) [115], reactive laser ablation [116] or reactive sputtering (SIROF) [117, 118]	High charge injection limit, low impedance, resistance to dissolution and corrosion in a saline environment [3, 4]	[88, 119] [115, 116] [117, 118]
	Gold	Sputtering	Deposition parameters have effect on metal adhesion and film structure (granular vs. columnar). Dense columnar films have lower impedance of the interface and increased charge injection properties	[85, 86]
	Gold Nanoparticle/CNT	Layer by layer	3-fold improvement in impedance and 1 order of magnitude increase in charge storage capacity	[120]
Conducting Polymer	PEDOT/Nafion composite	Facile electrochemical deposition	Average diffusion coefficient of hole carriers in the film 4.8×10^{-12} m^2/s	[121]
	PPy, PEDOT	Electrochemical deposition	High safe charge injection properties and good biocompatibility	[90]
	polyanilyne	In-situ polymerization	Low protein absorption/better biocompatibility and corrosion protection of pt electrode	[93]
	Conducting polymer nanotube	Electrochemical polymerization	Nano-structured polymer decrease the impedance of microelectrode by about two orders of magnitude and increase the charge transfer capacity by three orders of magnitude compared to polymer film	[122]
Carbon	Carbon nanotube (CNT)	Thermal/chemical vapor deposition	Safe and high charge injection limit with good cell adhesion/biocompatibility	[123, 124]
	Polypyrrole(PPy)/ graphene(GO)	Electrochemical deposition	The impedance of the PPy/GO coated Pt electrode is 10 % of the bare Pt electrode at 1 kHz and charge capacity density is more than two orders of the magnitude of Pt electrode	[94]
	Polypyrrole/CNT	Electrochemical deposition	High safe charge injection limit of 7.5 mC/cm^2 and low electrode impedance at 1 kHz along with good stability and neuro-compatibility	[95]

considerations for recording electrodes are, (1) maintaining consistent neural recordings for long term [21, 22] and (2) the quality of recordings. The distance and impedance between a neuron and electrode affect the quality of the recorded signals. For chronic implants, these two are affected by the brain's micro-motion [23, 24] and the thickness and composition of the connective tissue sheath surrounding the electrode, which may vary with time following implantation. Fabrication and design issues are certainly important for performance, however, addressing immunologic response resulted from surgical procedure [25] and brain's immune system [26–28] are two areas receiving a great deal of attention from the research community.

9.4.3 Sensing Electrodes

Sensing electrodes are tiny lab on a chip used to detect neurochemical and electrophysiological signals to understand the role of the specific chemical in normal and altered brain function. Chemical detection can be achieved by analyzing the in vivo cyclic voltammograms from electrode sites coated with ion selective membranes. The array of neurochemicals detected by voltammetric methods using sensing electrodes include dopamine [29–31], norepinephrine [32], serotonin [33–37], ascorbate [38, 39], uric acid [40], adenosine [41, 42], and acetylcholine [43].

The electrodes are predominantly made of very small diameter carbon nanofibers [44] coated by a thin layer of ion selective membrane that allow diffusion of analytes of interest to electrode surfaces. The membranes are made of organic polymers and include Nafion [45], fibronectin [46], base-hydrolyzed cellulose acetate (BCA) [47], polypyrrole [48], chitosan [49], and carbon nanotubes [33, 50]. Nafion is a material of interest because of its ease of deposition on Carbon fiber Micro-electrodes (CFM) surfaces, durability and its cation-selective permeability. Nafion is also resistant to electrode fouling [51] Base-hydrolyzed cellulose is also used as a fouling-resistant coating material for sensing electrodes because of its ability to exclude large biomolecules [47]. Fibronectin is another ion-sensitive coating materials with high biocompatiblity and chemical conductivity [44].

9.5 Electrode Characterization

An understanding of the electrochemical mechanisms, how neural stimulation and recording electrodes works at the electrode-tissue interface, is very important for the development of chronically implanted devices. Common techniques for characterizing electrochemical properties relevant to stimulation and recording will be discussed in this section [17]. The common techniques for electrochemical characterization of electrodes in neuroscience are cyclic voltammetry (CV), impedance spectroscopy, and potential transient measurements.

9.5.1 Cyclic Voltammetry

Cyclic voltammetry (CV) is a very useful technique that uses three-electrode measurement in which the potential of a test electrode, with respect to a noncurrent-carrying reference electrode, is swept cyclically at a constant rate between two potential limits. The current is allowed to flow between the test electrode and a counter electrode. The potential works as the driving force for reactions at the test electrode, while the rate of the reactions is proportional to the current. The information received from the CV is: (1) the presence and reversibility of electrochemical reactions, (2) the quantity of electroactive material on the electrode, and (3) the stability of the electrode. For a given electrode material CV response depends on variables like the sweep rate, the effective geometric area of the electrode, and the roughness/porosity of the electrode [17].

CV provides information about the charge storage capacity (CSC) of an electrode. The time integral of the cathodic current in a slow-sweep-rate cyclic voltammogram over a potential range within the water electrolysis window is equal to the CSC which is a measure of the total amount of charge available for a stimulation pulse. For Pt and Ir oxide electrodes, the water window is typically taken as −0.6–0.8 V with Ag|AgCl as the reference electrode. The shaded region in the AIROF CV in Fig. 9.5 represents a CSC of 35 mC cm^{-2}, calculated at a sweep rate of 50 mV s^{-1} [52].

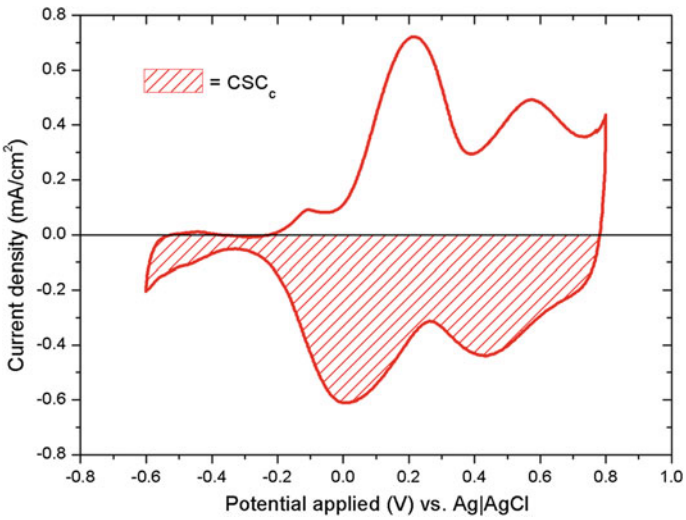

Fig. 9.5 Charge storage capacity (*CSC*) from cyclic voltammetry of IrO_2 electrodes

9.5.2 Impedance Spectroscopy

Electrochemical impedance spectroscopy (EIS) provides useful information about the recording capability of an electrode by measuring the electrical impedance and phase angle obtained with sinusoidal voltage or current excitation of the electrode. It is also helpful to estimate the resistive contribution of tissue conductivity to the overall electrode impedance. The measurement is made over a broad frequency range, typically $<1–10^5$ Hz. A linear current–voltage response is obtained at each frequency. For voltage excitation, the root-mean-square magnitude of the excitation source is typically ~ 10 mV, not exceeding 50 mV. EIS is a safe method for the in vivo assessment of an electrode.

9.5.3 Voltage Transients

Voltage transient measurements estimate the maximum charge that can be injected in a current-controlled stimulation pulse. The experimental setup consists of a three electrode configuration with a test electrode, a large-area return electrode and a noncurrent-carrying reference electrode. The voltage transients are analyzed to determine the maximum polarization, both the most negative (E_{mc}) and most positive (E_{ma}), across the electrode–electrolyte interface which are then compared with established maximum safe potentials to polarize the electrode.

9.6 Substrate and Encapsulation Materials

In this section, various state of the art substrate and encapsulation materials are discussed. Substrate refers to the mechanical structure that supports the entire electrode components including interconnecting metal lines, thin film interlayers, encapsulating materials, etc. Encapsulation refers to the layer of insulating materials that is deposited to isolate metal electrodes from neural environments. Both the substrate and encapsulation materials have to be biocompatible, biostable and possess good dielectric properties. A material is said to be biocompatible if it does not induce a toxic, allergic or immunologic reaction. Similarly, a good biostable material must not change physically or chemically under the influence of any biological fluids or metabolic substances.

The very common and widely used substrate materials are silicon (Si) and glass for rigid neural electrodes where silicon dioxide (SiO_2) and silicon nitride (Si_3N_4) are used as protective or encapsulation layers. The recent trend is to develop polymer based flexible electrodes that can deform easily to contour the brain environment. The flexible electrodes are being adopted to avoid or reduce tissue damage, inflammatory reaction, scar formations, and micromotion caused by rigid

electrodes [21, 53]. Different polymeric materials such as polyimide [54, 55] benzocyclobutene (BCB) [56], polydimethylesicloxane (PDMS) [5, 57, 58] and parylene [59, 60] are recently being investigated as both substrate and encapsulations materials. Polyimide is a proven biocompatible material with appropriate mechanical properties for ease of insertion and good adhesion with metal. The major disadvantage of polyimide is its permeability to environmental moisture and ions that could lead to the loss of its dielectric property causing short circuiting. Hence long term use of polyimide based devices may be questionable. Due to its low moisture absorption and chemical stability, BCB has been studied for potential substrate and encapsulation material. A thermoplastic material parylene and a rubber based material PDMS are both superior materials due to their excellent biocompatibility and very low moisture absorption. However, parylene is gaining more interests due to its ease of manufacturing through room temperature vapor deposition process. Thus the parylene based structure can be very conformal coated with almost no residual stress. The major disadvantage of this material is its poor adhesion with some metals. To promote adhesion, a secondary barrier material such as chromium [21, 53] can be used.

9.7 Current State of the Art Electrodes

The research efforts in the development of brain implantable microelectrode are driven by the following factors:

1. Single site electrode to multisite electrode for better efficiency
2. Rigid substrate to flexible substrate to match the brain's mechanical properties
3. Smaller geometry and higher charge injection properties
4. Biocompatibility
5. Corrosion/degradation, water absorption, swelling
6. Immune response and associated decrease in performance.

A comprehensive review of the literature on treatments involving electrical stimulation of neural tissue is presented in the reviews by Li and Mogul [61], Normann [62], Perlmutter and Mink [63], Clark [64], Shepherd and McCreery [65], Jackson et al. [66], Rutten [67], Jezernik et al. [68], Prochazka et al. [69], Hoffer et al. [70]. A very informative discussion on the foreign-body response to implanted electrodes and potential adverse consequences is provided in the review by Polikov et al. [21]. Table 9.2 below contains brief information about very recent research and findings that addressed the above mentioned problems. From the materials selection point, the most suitable materials can be categorized into three major types;

1. Metal: Pt, IrO_x, gold etc., primarily deposited by sputtering technique.
2. Carbon: CNT, Graphene etc., primarily deposited by chemical vapor deposition.
3. Conducting polymers: PPy, PEDOT, Polyanilyne etc., primarily fabricated by electrochemical deposition or insitu polymerization.

9.7.1 Metallic Electrodes

Platinum is the most widely used and biocompatible material used in electrodes for neural implants [71]. It is used as the structural material of the electrode in bulk form and as thin film electrode on other substrate material as well [17]. Among other novel electrode materials that have been widely studied, IrO_2 is the most promising candidate material for development of neural prostheses. Iridium oxide was found to be having very high charge injection limit with minimum power consumption [72, 73]. It delivers charge in faradic mechanism and the reversible reaction does not form a toxic interface with the neurons [74]. It is possible to deposit very thin film of IrO_2 both in crystalline and amorphous form using vapor deposition techniques [75, 76] on different substrates. Biocompatibility of sputtered deposited IrO_2 has been extensively studied in vitro and found biocompatible with cultured neurons [77–79].

9.7.2 Carbon Nanotube Electrodes

It is discussed in the previous section that various biocompatible and biostable metallic materials such as gold and platinum have been used for years as electrode materials. However, as the electrode size becomes smaller, the electrode impedance increases significantly causing ineffective neural recording and stimulation. To overcome this problem, carbon nanofibers (CNF) and carbon nanotube (CNT) [77, 80] based electrodes are getting attention due to its intriguing physicochemical properties. They are also the materials of choice for creating nanoscale topography. Many groups [81–83] have studied the cytotoxicity of carbon nanofibers with neuronal cells.

The CNT electrodes are shown to improve electrode characteristics because of the fact that the nanoscale CNTs have very high surface to volume ratio that increases the effective interfacial area thereby reducing electrode impedance. Moreover, CNTs have been demonstrated to be a good biocompatible and biostable material with improved neural activity and neuronal growth. The material is highly electrically conductive and exhibits effective electrical stimulation with long-term endurance; hence CNT electrodes can be used for chronic neural recordings or stimulations. CNTs are typically grown on metal conductors using chemical vapor deposition (CVD) process. To create well aligned CNTs, a very high temperature is to be maintained (typically around 650°) in the CVD chamber [78]. Hence, CNT based electrodes have been successfully created only using rigid substrates such as silicon or glass that can withstand the high temperature required for a CVD process. Since the most of the flexible substrates are based on polymer that have relatively low melting or decomposition temperatures, high temperature CVD is not suitable to grow CNTs on flexible substrates. There are several alternative techniques of creating CNT microelectrodes on flexible substrates such as transferring well-grown CNTs to flexible substrates by microwave welding, stamp transfer, polymer binding

and electrodeposition coating. However, these techniques do not always ensure good adhesion between the CNTs and the substrate; thus caution has to be taken for long term applicability of these electrodes. Recently, CNTs have been successfully grown on metal surface of polyimide substrate based microelectrodes using low temperature (400 °C) CVD process. This method seems highly compatible with the flexible microelectrode fabrication process and will be explained in a later section.

9.7.3 Conducting Polymer Electrodes

The conducting polymers (CP) or carbon derivatives are usually deposited on a metal primarily on Platinum electrode to enhance the charge injection properties and corrosion properties. Schimdt group is a pioneer in studying conductive polymers as a candidate for thin film neural electrode [84]. CPs including polypyrrole (PPy), polythiophene (PTh) and PTh derivative poly(ethylene dioxythiophene) (PEDOT) are being studied for improved long-term efficacy and performance of both neural stimulation and recording electrodes. The main characteristic of CPs is a conjugated backbone with high degree of π-orbital overlap. This structure can be modified by acceptor or donor electrons (also called oxidation or reduction, respectively) thereby creating p-type or n-type materials, respectively. It has been observed that electrical conductivities of a polymer can be improved by as much as 15 orders of magnitude by changing just dopant concentrations.

The following section discusses several of the fabrication techniques in brief.

9.8 Fabrication of Thin Film Electrodes

It is mentioned in the Sect. 9.7.3 that there are many methods to fabricate neural electrodes depending upon the electrode configurations and type of surface coatings. In most cases, the electrodes are fabricated layer-by-layer deposition of thin films. Thin electrode films are then patterned and etched using conventional photolithography process to create electrodes with certain configurations. In this section, common thin film deposition processes are discussed. Then a common technique used in fabricating flexible electrodes is briefly presented.

9.8.1 Common Thin Film Deposition Processes

9.8.1.1 Sputtering

Various metallic materials such as platinum (Pt), iridium oxide (IrOx), gold (Au), etc. are deposited using a physical vapor deposition (PVD) method called sputtering. A schematic representation of the technique is shown in Fig. 9.6. The method

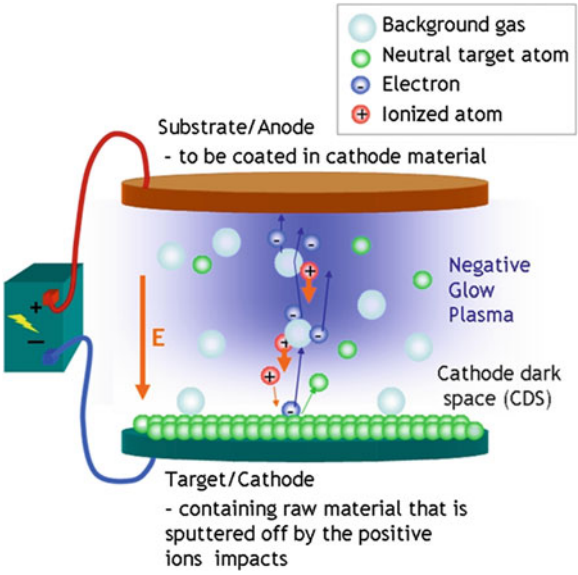

Fig. 9.6 A schematic diagram of DC plasma sputtering (*Source* http://upload.wikimedia.org/wikipedia/commons/2/2a/DCplasmaSputtering.jpg)

involves ejecting material from a "target" that is to be deposited onto a "substrate" by bombarding the target surface with neutral target atoms. Substrate materials can be of any shape however, free from small steps such as planar silicon or micro-scale Kevler fiber [85, 86]. Ionized sputtered particles fly from the target and impact on the substrates or vacuum chamber. To facilitate ion movement, chamber gas pressure is controlled depending upon the type of target materials and required coating morphology. At higher gas pressures, the ions collide with the gas atoms that act as a moderator and move diffusively, reaching the substrates or vacuum chamber wall and condensing after undergoing a random walk. The sputtering gas is often an inert gas such as argon. Researchers have spent years to identify critical process parameters such as gas pressure, RF power, deposition time, etc. for creating coatings with required surface morphology, microstructure and thickness [85]. Although the process is complex due to the presence of many process parameters, experts have large degree of control over the growth and microstructure of the film.

Adhesion between the substrate material and the metal coating is very critical for the neural applications as long term implanting may result in delamination thereby causing implant failure. The substrate surfaces are usually cleaned sequentially prior to deposition using acetone, methanol, isopropanol, and DI water to remove particles and organic residues [85–88] to promote adhesion. In many cases, the adhesion between the electrode material and the substrate material is enhanced by adding an interlayer between them. For example, a thin layer of titanium can be used to promote adhesion of the gold films to silicon substrates [85].

9.8.1.2 Electrochemical Deposition/Polymerization

Electroactive conducting polymers such as polypyrrole (PPy) [89], PEDOT [90–92], polyanilyne [93] and their composites such as PPy/graphene oxide (GO) [94], PPy/carbon nanotube [95] are used to modify metallic electrode surfaces using electrochemical deposition process. Such surface modifications are to (1) improve sensitivity; (2) impart selectivity; (3) suppress the effect of interfering reactions; and (4) immobilize indicator molecules [96]. Electrochemical deposition of polymer is often called as electrochemical polymerization.

In general, electrochemical deposition of polymer is done using electrochemical polymerization equipment. A schematic diagram of the equipment is shown in Fig. 9.7. The monomer compound of the polymer to be deposited is first dissolved into a solvent containing a suitable supporting electrolyte. An appropriate voltage is applied to the electrode pair that are being immersed into the electrolyte solution. The monomer is oxidized or reduced to create polymer that is deposited in the form of powder or a film on the surface of the anode or cathode, respectively. If the monomer is oxidized and polymerized on the anode surface, it is called an electrochemical oxidation polymerization. On the other hand if the monomer is reduced and polymerized on the surface of the cathode, it is called electrochemical reduction polymerization. The reference electrode may or may not be necessary for all types of films.

The type of polymer to be deposited on anode or cathode surface depends on the composition of electrolyte, solvent type, electrode type, and monomer. A list of various thin film polymers deposited on different electrode materials are shown in Table 9.3. Other parameters that may influence the deposited film quality are the composition of the electrolyte, the applied voltage, the current density, distance between electrodes, and the polymerization temperature [91].

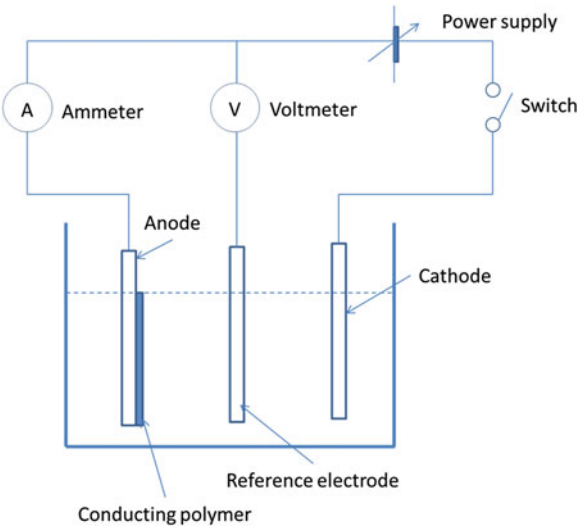

Fig. 9.7 A schematic diagram of electrochemical deposition setup (oxidation type)

Table 9.3 A list of various thin film polymers deposited on different electrode materials

Film to be deposited	Substrate/backbone material/film electrode	Counter electrode	Reference electrode	Monomer	Supporting electrolyte	Reference
PEDOT	Conductive glass	Nickel (Ni) plate	Silver (Ag) wire	0.1 mol/l 3, 4-ethylenedioxytiophene (EDOT)	Four-fluorinated boric acid tetrabutylammonium tetrafluoroborate (TBAFB4)	[91]
Ppy	Aluminum or Al 2024-T3	Platinum plate	Ag/AgCl	0.05 M pyrrole	0.05 M Tiron or 0.05 M Na-*p*TS	[89]
PPy/ Poly(vinyl alcohol (PVA)	ITO coated glass with spin coated PVA on it	Ni plate	Ag wire	0.1 mol/l pyrrole	$TBAFB_4$	[125]
Ppy/GO	Platinum (Pt)	Pt foil	Pt foil	0.05 mol/l pyrrole	Aquas solution of 0.05 mol/l poly(sodium 4-styrene-sulphonate) (PSS) and 0.5 or 1.0 gm/l GO	[94]
Paratoluene sulphonate (pTS) doped PEDOT	Pt	Pt	–	0.1 M EDOT	Aquas solution of acetonitrile with 0.05 M pTS dopant	[126]

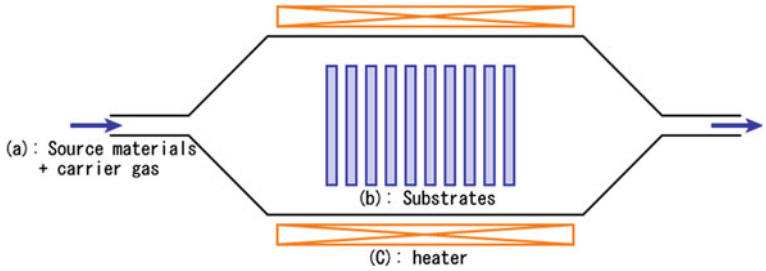

Fig. 9.8 A schematic diagram showing a typical CVD process (*Source* http://upload.wikimedia.org/wikipedia/commons/9/9e/ThermalCVD.PNG)

9.8.1.3 Chemical Vapor Deposition

Chemical vapor deposition (CVD) (see Fig. 9.8) is a chemical process to deposit high-purity thin film on a substrate. One or more precursor gases are delivered into a reaction chamber at approximately ambient temperature. The substrate that is subjected to be thin-film deposited is maintained a high temperature that depends on the type of deposited material. As precursor gases pass over or come into contact with the heated substrate, they react or decompose forming a solid phase that is deposited onto the substrate. Volatile by-products produced in the process are removed by gas flow through the reaction chamber. CVD processes are widely used in the microfabrication industry to deposit various metallic thin films such as molybdenum, tantalum, titanium, nickel, and tungsten. In general, for an arbitrary metal *M* the precursor gases used are metal chloride (MCl_5) and hydrogen (H2) that undergo the following chemical reaction to create M film:

$$2MCl_5 + 5H_2 \rightarrow 2M + 10HCl$$

Currently, the CVD process is also being used to deposit CNT thin films on metal surface for neural electrodes. In this case, a mixture of C_2H_2 and H_2 is used as a precursor gas.

9.8.2 Flexible Electrode Fabrication

A crystalline polymer parylene-C has received tremendous attention due to its unique combination of physical, chemical, and mechanical properties. It is being used as both structural and encapsulation materials because of its improved biocompatibility and inertness, [53, 59]. Due to the poor adhesion of parylene to metallic materials, a thin layer of interlayer can be used to improve adhesion between them [60]. A simple two-mask photolithography based fabrication process of a microelectrode arrays is shown schematically in Fig. 9.9 [53].

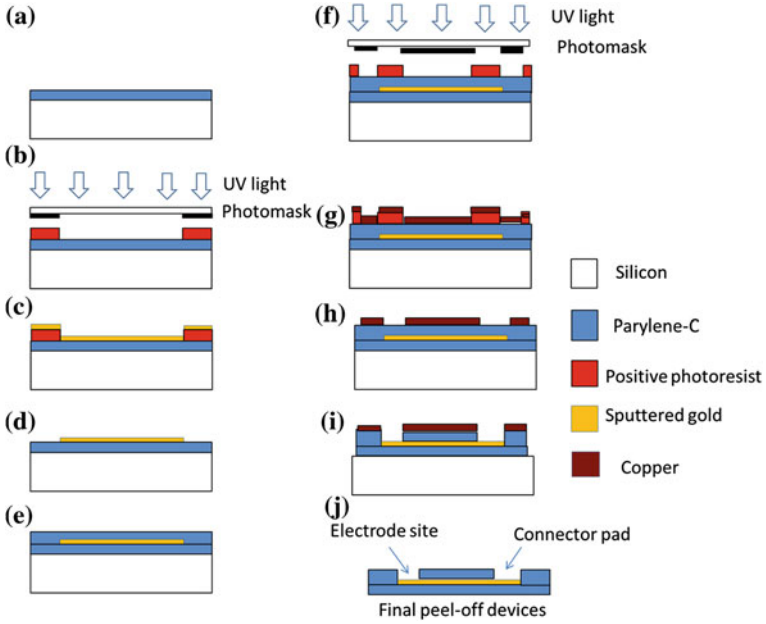

Fig. 9.9 Fabrication steps of flexible microelectrode arrays

In the first step, silicon substrate is vapor deposited with parylene-C (Fig. 9.9a). To create the array geometry, a positive photoresist is spun over parylene followed by photo-exposure and development (Fig. 9.9b). Sputtering technique is then used to successively deposit chromium and gold on parylene (Fig. 9.9c). Chromium is used in this case to promote adhesion between gold and parylene. The unwanted metal is then removed using lift-off technique where the wafer is sonicated in an acetone bath (Fig. 9.9d). A second layer of parylene is deposited next on the entire wafer surface to encapsulate the patterned metal lines. The next several steps (Fig. 9.9f–i) are used to selectively remove parylene thereby exposing metal surfaces for recording sites and interconnecting bond pads. First, a thin positive photoresist layer is spun, exposed, and developed (Fig. 9.9f). A thin copper layer is then deposited using sputtering technique (Fig. 9.9g) that is later used as a parylene etch mask. The unwanted copper is then lifted-off thereby creating electrode outline and openings for recording sites and bond pads (Fig. 9.9h). Reactive ion etching of parylene is carried out to remove it from not only the recording sites and bond pads, but also from edges to define the final outline of the device (Fig. 9.9i). After wet-etching of copper, the devices are manually peeled off from the wafer surface (Fig. 9.9j).

Similar processing steps have also been adopted to create polyimide based flexible microelectrodes [54]. In this case, glass slide is used as handle substrate and sputtered titanium/platinum is used as electrode material. For both the

parylene and polyimide based electrodes, the exposed recording sites can be coated with conducting polymer, CNT, polymer nanotube, etc. to have further improvement in neuronal cell response.

9.8.3 CNT Electrode Fabrication

It is discussed previously that CVD based fabrication of CNT electrode requires high temperature substrate materials. Recently, researchers [80] were successfully able to deposit CNT film on metal at relatively low temperature (400 °C). Since polyimide (PI) melting point is around 550 °C, CNT electrode can be fabricated using polyimide as a substrate material. Figure 9.10 illustrates the process flow of fabricating CNT microelectrodes on a PI substrate. The process steps are described as follows. A thin layer of adhesion layer followed by a layer of gold (Au) are deposited on PI film (Fig. 9.10a). Both layers are then patterned to form microelectrodes, interconnecting wires, and bond pads (Fig. 9.10b–d). A titanium (Ti) adhesion layer followed by a thin catalyst layer of nickel (Ni) are deposited using a shadow mask having openings only above microelectrode sites (Fig. 9.10e). The Ni catalyst layer is used to promote adhesion between CNTs and the metal electrode surface. This adhesion is critical for long term stability of the CNT layer in neural environment. Then, CNTs are grown above the Ni catalyst by thermal CVD with using C_2H_2/H_2 as precursor gases. Finally, all regions except for the electrode areas and the wire-bonding pads are encapsulated by a relatively thick layer of electrochemically deposited parylene.

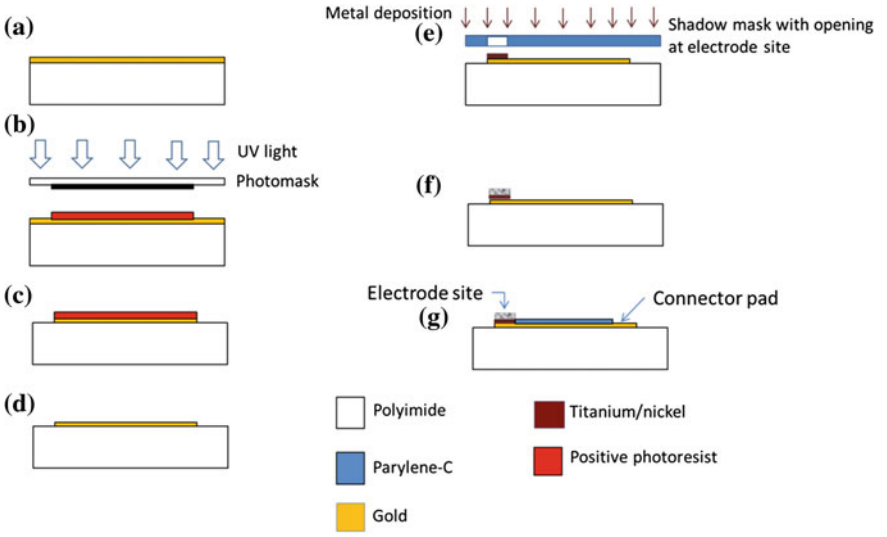

Fig. 9.10 Fabrication steps of CNT electrode for flexible microelectrode arrays (adapted from Ref. [80])

9.9 Degradation of Thin Film Electrodes in Neural Environment

The major drawback of thin film microelectrodes is they are prone to degradation in chronic application. This section reviews the degradation mechanism of the common thin film coatings used in brain implantable microelectrodes.

Electrolysis of water is the most common irreversible processes responsible for platinum electrode dissolution due to the oxidative formation of soluble metal complexes coupled with pH changes and gas formation. Oxidation of organics, such as glucose and tyrosine, and saline oxidation, have been identified, as other possible irreversible or harmful electrochemical reactions that might be responsible for degradation [10, 11] of implanted neural stimulation electrodes like Pt dissolution [11, 97] and iridium oxide delamination [98]. It is important to establish the maximum charge density for stimulation specific to the thin film material. It has been found that application of current pulse higher than a safe maximum results in polarization of the IrO_2 electrode beyond the potential window for electrolysis of water (−0.6–0.8 V versus Ag|AgCl) and delamination of the film [98].

For thin film conductive polymer electrodes, water absorption and volume change due to mass transport are possible reasons of degradation [99]. A comparison between electrodeposited PPy/Cl, PPy/PSS and PPy/SWCNT films on Pt after stimulation showed a significant delamination for PPy/Cl films after stimulation. PPy/PSS films did not show significant delamination, but the edge of the film was swollen and noticeably deformed [95]. The volume change due to electrode cycling may result in adhesion failure of the conducting polymer films on the electrode substrate [100].

9.10 Biocompatibility Testing

To achieve functionality and reliability of the device, interaction of the brain cells with the device at the interface must be studied with respect to biocompatibility. Before any experiments with these neural implant devices are conducted in living animals, characterization should be conducted upon cultured cells. Cell viability is a preliminary study of biocompatibility. Therefore, culturing of cells on the proposed materials is essential to test the cytotoxicity.

However, the concept of biocompatibility is not limited to non-toxicity, but encloses a wide spectrum of physical and chemical surface properties and whole behavioral aspects in the biological environment around the implant as well. Therefore, three areas need to be considered [101]:

- The bio-safety which include body's response to the electrode
- The bio-functionality which include the electrodes performance in the body

Table 9.4 FDA suggested tests of initial evaluation of biocompatibility

Device categories			Biological effect							
Body contact		Contact duration: A-limited (<24 h) B-prolonged (24 h to 30 days) C-permanent (>30 days)	Cytotoxicity	Sensitization	Irritation or intra-cutaneous reactivity	System toxicity (acute)	Sub-chronic toxicity (sub-acute)	Genotoxicity	Implantation	Haemocompatibility
Implant device	Tissue/bone	A	X	X	X	O	–	–	–	X
		B	X	X	O	O	O	X	X	–
		C	X	X	O	O	O	X	X	–
	Blood	A	X	X	X	X	–	–	X	X
		B	X	X	X	X	O	X	X	X
		C	X	X	X	X	X	X	X	X

Table 9.5 Some additional tests suggested by FDA

Device categories			Biological effect			
Body contact		Contact duration: A-limited (<24 h) B-prolonged (24 h to 30 days) C-permanent (>30 days)	Chronic toxicity	Carcinogenicity	Reproductive/ developmental	Biodegradable
Implant device	Tissue/ bone	A				
		B				
		C	X	X		X
	Blood	A				
		B				
		C	X	X		X

X ISO evaluation tests for consideration
O Additional tests which may be applicable

- In addition, bio-stability is important since the implant must not be susceptible to attack of biological fluids, proteases, macrophages or any substances of metabolism. Stability of implant material is important not only for stable function, but also because degradation products may be harmful for the host organism.

All these aspects of biocompatibility should be investigated in culture before any material or device can be tested in vivo. For the development of an implantable neural electrode the general tests of biocompatibility consists of the following steps:

- in vitro
- in vivo testing
- animal models
- cytotoxicity

The information presented in Tables 9.4 and 9.5 are taken from the website of the US Food and Drug administration (FDA: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080742.htm) that entails the general guideline for the initial evaluation tests for any medical device biocompatibility.

9.11 Conclusions

Key materials for thin film coatings for microelectrodes are Pt, IrO_x and gold. These systems use microelectronic fabrication technique such as sputtering and can be mass produced. Conductive polymers such as PEDOT and gold coated Parylene are very good options. PEDOT is utilized via electrochemical deposition while gold coating can be accomplished on Parylene using sputtering. Carbon nanotube systems can be developed via thermal/chemical vapor deposition. Other coating materials discussed in the article have good potential. However, their efficacy is closely tied to acute microelectrode applications. Chronic applications require more stable material systems as the ones mentioned above. Biocompatibility of all of these materials require further evaluation for their long-term application in neural devices.

9.12 Future Trends

Chronic neural stimulation requires highly stable microelectrode and biocompatible materials with high charge injection capability. Conductive polymers coating is a major trend that must be exploited that meets these goals. Conductive polymer, poly (3,4-ethylenedioxythiophene) PEDOT has excellent promise as it has charge injection limit similar to IrO_x. Well-coated PEDOT electrodes can be very stable under chronic stimulation conditions, suggesting that PEDOT is a promising electrode material to be further developed for chronic neural stimulation applications. Parylene-C shows promise as selective insulation of microelectrodes to provide greater intensity at the electrode probes for neural activity. Flexibility of Parylene has also been exploited for micro channeling for drug delivery. Chemical vapor deposited Parylene-C films show potential for implantable dielectric encapsulation material. Gold-coated parylene is an important trend in new neural devices. Gold with CNT can increase sensitivity several fold.

Finally, carbon nanotube modified microelectrodes have been used to increase the sensitivity, promote electron transfer, and reduce cell coverage or fouling. Most methods have focused on nanotube coatings of somewhat larger electrodes and slower electrochemical techniques that are not good for measurements in vivo. However, nanotube modified coatings will continue to offer new coating designs and offers the potential for tailored systems for superior microelectrode performance, both from optimizing electrochemical property improvements and also from durability for chronic implantation.

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