Electrochemistry in Neural Stimulation by Biomedical Implants

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Abstract: Advances in biomedical engineering, micro-fabrication technology, and neuroscience have led to many novel and improved biomedical implants for electrical neural stimulation to restore human function and improve the quality of human life. Some examples of such biomedical devices are cochlear implants, visual implants, deep brain stimulators and spinal cord stimulators. One of the key components of biomedical implants is the stimulating electrodes. The electrodes, when in contact with living tissue, form an interface between the electronic device and the biological tissue. This paper reviews electrochemical aspects of neural stimulation implants. A brief introduction on the developments of biomedical implants is presented. The basis for electrical stimulation and the fundamental mechanisms of charge injection at the electrode/tissue interface are introduced. A survey of the most commonly used electrode materials and methods in the fabrication of microelectrodes is given. Some electrochemical related challenges for the development of medical implants, such as electrode reactions, impedance, charge injection capability, electrode corrosion and biocompatibility are discussed. In addition, microsensors and microbiosensors for possible applications in biomedical implants are reviewed. The challenges in the development of chronic implantable sensors for medical implants are also discussed. A better understanding of design issues and challenges may encourage interdisciplinary efforts including more contributions from electrochemists to push forward the development of neural stimulation biomedical implants.

Key words: neural stimulation; biomedical implants; electrode/tissue interface

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1　Introduction

Biomedical implants for electrical neural stimulations have been used widely for many decades to restore main functions of nervous systems for patients with neural damage. They play a major role in replacing or improving the function of every major body system to maintain a good quality of life. Some common implants include cardiac pacemakers and defibrillators[1], neural prostheses such as spinal cord stimulators[2], deep brain stimulators[3] and cochlear implants[4]. Novel neural prostheses, such as retinal prostheses[5] and brain-machine interfaces[6], with higher resolution and site specificity are being actively investigated. These devices require larger numbers of microelectrodes patterned in a very small area, more sophisticated circuit designs, and longer lifespans. Electrochemistry and electrochemists play a key role in the development of biomedical implants for electrical neural stimulations.

2　Biomedical Implants

Biomedical implants for neural stimulation are active microelectronic stimulators. They typically consist of an external part positioned outside the body and an internal part implanted inside the body. The

implants commonly contain a stimulator to generate stimulation pulses and for system control, an antenna for data/power transfer and an electrode array for stimulation. Two modern implants, cochlear implants and visual (retinal) implants, are good examples to illustrate the functional mechanism of neural stimulators.

2.1　Cochlear Implants

A cochlear implant is designed to use electric stimulation to provide or restore functional hearing in totally deafened patients. A cochlear implant consists of an electrode array that is inserted into the cochlea and designed to electrically stimulate the remaining nerve fibers. Figure 1 shows a schematic of a typical cochlear implant system[7]. Sound is picked up by an external microphone and processed in an external sound processor into a digital signal. It is transmitted through a telemetry interface (an external antenna) via a radio frequency signal across the skin to a receiver (an internal antenna) linked to a stimulator which is implanted in a bony bed in the skull behind the ear. The external antenna is held in place by a magnet attracted and aligned to the internal antenna under the skin. The hermetically sealed stimulator implanted on the skull contains active electronic circuits that derive power from the RF signal, decode the digital sound signal, convert it into electric stimulation currents, and send them along cable wires to electrode arrays in the cochlea. The electrodes aligned along the tonotopic gradient (frequency distribution of sound) of the cochlea stimulate the auditory nerve which is connected to the central nervous system in the brain, where the electrical impulses are interpreted as sound[4].

Some early cochlear implants contain low electrode counts, usually 1 to 7 electrodes. Typical modern cochlear implants on the market contain 16 to 22 electrodes made of platinum or platinum-iridium alloys molded into a carrier of silicone body[8]. The challenges in the development of electrode arrays include deeper insertion into the cochlea to better match the tonotopic gradient of stimulation to the frequency band assigned to each electrode channel, improving
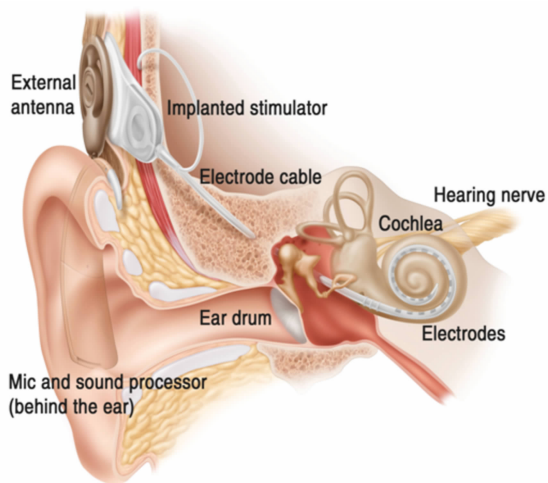

Fig. 1　An example of a modern cochlear implant system that converts sound to electric impulses delivered to the auditory nerve through an electrode array implanted within the cochlea[7]

efficiency of stimulation and reducing insertion related trauma or tissue damage.

2.2　Visual Implants

Inspired by the success of cochlear implants, research efforts worldwide are developing microelectronic visual prostheses (visual implants) aimed at restoring vision for the blind. Various visual prostheses using neural stimulation techniques targeting different locations along the visual pathway such as the retina[5], optic nerve[9] and visual cortex[10] are being pursued. Among them, retinal prostheses have proved to be capable of offering blind subjects in advanced stages of outer retinal diseases the opportunity to regain some visual function.

Fig. 2a shows a schematic of a retinal implant design. In this design, a small camera is housed in a pair of glasses which captures images such as letter "E", and then wirelessly transmits this data after coded by an external video processor to an implantable electronic stimulator. The stimulator then stimulates the remaining nerve cells of the retina of a blind patient through an implanted electrode array. The retinal neurons relay the electrical impulses via the optical nerve to the brain, where the electrical impulses are interpreted as vision. Fig. 2b shows an electrode array made of 60 Pt electrodes in thin-film polyimide
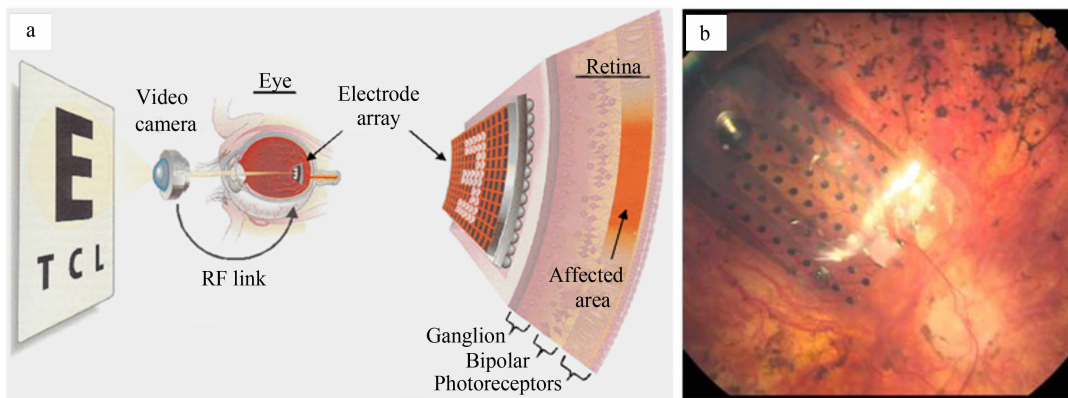
Fig. 2 A schematic of a retinal implant design(a) and a thin-film polyimide 60 Pt electrodes array from Argus™ II Retinal Prosthesis in the eye of a human subject[5](b)

from the world's first commercial retinal implant, the Argus™ II Retinal Prosthesis System[5].

3 Electrochemical Aspects of Neural Stimulation by Biomedical Implants

Neural stimulation electrodes, when in contact with living tissue, form an interface between the electronic device and the biological tissue. The neural stimulation processes using electrodes are electrochemical in nature. While basic electrochemical principles, developed mainly through slow DC experiments, are useful for biomedical implant developments, some limitations and challenges remain due to the biological systems involved and the high frequency pulses required.

3.1 Electrical Stimulation of Biological Tissue

Electrical neural stimulation relies on depolarizing the membranes of excitable cells through a voltage gradient across the semi-permeable cell membrane established between electrodes[11]. The voltage gradient is achieved by either applying constant voltage pulses or constant current pulses to generate the injectable current or charge required to excite neural cells. Voltage pulse based systems require a simple electronic circuit design while the current pulse systems require a complicated circuit design but provide better output current control. As a simple example of monopolar stimulation, a microelectrode is placed in

the vicinity of excitable tissue. Current runs from the small stimulation electrode, through the extracellular fluid surrounding the tissue of interest, and finally to a distant large counter electrode[12].

3.2 Charge Injection Mechanisms

Electrical stimulation of biological tissue with metal electrodes requires the flow of ionic charge in the biological tissue. This flow of charge can be achieved through both faradaic and non-faradaic mechanisms at the interface of the electrode/tissue surface[12]. Fig. 3 shows a simplified equivalent circuit of the electrode/electrolyte interface[13]. The faradaic mechanism of charge injection involves electron transfer across the electrode-tissue interface. For some
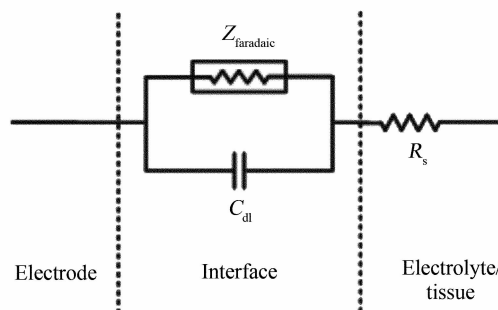

Fig. 3 Equivalent circuit model of electrode/tissue interface in neural stimulation
$Z_{faradaic}$: faradaic impedance represents faradaic charge injection processes, C_{dl}: double layer capacitance represents charging/discharging capacitive (non-faradaic) charge injection processes, R_s: electrolyte solution or tissue resistance[13]

metal oxides, charge stored can be recovered through reversible reduction reactions. Such reversible metal oxidation and reduction processes can be used for safe neural stimulation. If charge density is too high for a given electrode, irreversible electrochemical reactions such as metal corrosion or dissolution, gas evolution, or production of toxic chemical reaction products can occur. Such induced harmful electrochemical reactions during faradaic charge transfer not only cause electrode damage, but also can cause tissue or nerve damage.

The non-faradaic (capacitive) mechanism involves charging or discharging of the electrochemical double layer. Capacitive mechanism is an ideal mechanism of charge injection because no electrochemical reactions can occur in the electrode/tissue interface. Ions in the tissue are attracted or repelled by charge on the electrode to produce pulses of ionic current. There is no net charge transfer across the electrode/tissue interface. A higher capacitance is favorable for a stimulation electrode. For a given electrode, capacitance C, is calculated according to the equation:

$$C = \varepsilon\varepsilon^{\circ}(A/d) \tag{1}$$

where ε is the dielectric constant of the solvent, ε° the permittivity in vacuum, A the electrochemical surface area of the electrode surface, and d the thickness of the dielectric layer.

As one can see from Equation 1, the real surface area of the electrode is a key factor to achieve large charge storage capacity for a given material and device design: the higher the surface area, the higher the capacitance. For high density microelectrode arrays used in neural stimulation, the geometric surface area is often limited by the application. An effective way to increase the electrochemical surface area without enlarging array size is to increase the surface roughness of the electrode.

3.3　Neural Stimulation Pulses

Most neural stimulation applications use a biphasic, charge-balanced, cathodic-first current pulse as shown in Fig. 4a. The cathodic phase is believed to be more effective in exciting cells or neurons than the anodic phase since it requires less current to depolarize cells and to reach the stimulation threshold[12,14]. When using a biphasic current pulse, the electrode response is similar to that in a current step experiment or in a constant current reversal chronopotentiometry[15], except that the neural stimulation is carried out at very high frequency with a very short pulse width.

A typical voltage response or voltage excursion under such pulse current is shown in Figure 4b. After the cathodic phase, electrodes are biased negatively. A reversal anodic current phase will remove such negative bias and keep the electrode voltage near neutral. While typical biphasic pulse maintains charge balance using symmetric phases ($i_a \cdot t_a = i_c \cdot t_c$; $i_a =$
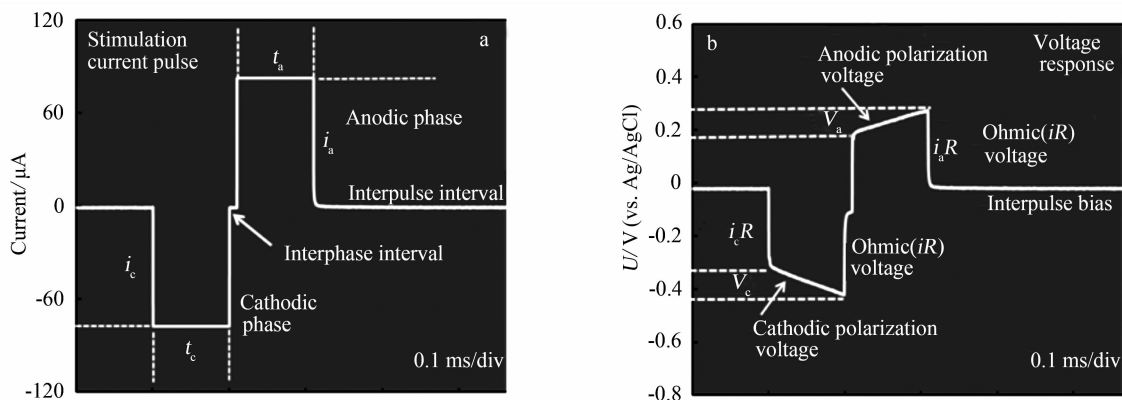

Fig. 4　A charge-balanced, cathodic-first, biphasic pulse current(a) and the voltage response or excursion of an electrode under the pulse current[16] (b)

i_c & $t_a = t_c$), asymmetric phases ($i_a \cdot t_a = i_c \cdot t_c$; $i_a \neq i_c$ & $t_a \neq t_c$) are also used depending on applications. This biphasic method minimizes electrode polarization by the charge-balancing second phase, which cancels out cathodic bias and maximizes charge delivery. During each phase, electrodes are subjected to charges that may exceed their charge-delivery capabilities. Electrode materials used for chronic stimulation are required to maintain high charge delivery capability and low voltage excursion.

The voltage response of an electrode under pulse current stimulation is a direct indicator of its charge injection capability[16]. For a given pulse current, the electrode that shows lower and linear polarization voltage presents higher charge injection capability and less effect from irreversible electrochemical reactions. These irreversible reactions may produce harmful by-products and/or cause electrode corrosion. The voltage excursion curves of a smooth Pt electrode and an electroplated rough Pt electrode are compared in Fig. 5. The electrodes were stimulated in phosphate-buffered saline (PBS) at various charge densities at 50 Hz. Because of the lower impedance and higher charge capacity of the rough Pt layer, polarization voltage across the electrode under stimulation is lower than the thin-film smooth Pt electrode and the excursion profile is linear. Based on voltage excursion un-der pulse stimulation currents, the charge injection limit or charge injection capacity (Q_{inj}) of a stimulation electrode can be determined. Q_{inj} is defined as the maximum cathodic charge that resulted in electrode voltage to exceed 0.6 V versus Ag/AgCl.

At low injected charge density or at the early stage of a stimulation pulse, charge injection is dominated by charging and discharging of the double layer. At high injected charge density or at the prolonged stimulation pulse, faradaic reactions will dominate charge transfer. To fully utilize charging/discharging currents, it is best to keep the pulse width narrow[12,14]. However, the pulse width is often limited by stimulator circuit design and by applications. For example, stimulation for hearing applications typically requires very narrow pulses in the tens of microseconds while visual stimulation requires longer pulses in the hundreds of microseconds.

3.4　Neural Stimulation Electrode Materials

In neural prosthetics, the demand for high performance, high-resolution microelectrodes is increasing as more and more neural prosthetic devices are developed. The choice of electrode materials has become a key factor for the success of such neural prostheses. The electrodes must be made smaller to spatial resolution and at the same time deliver adequate
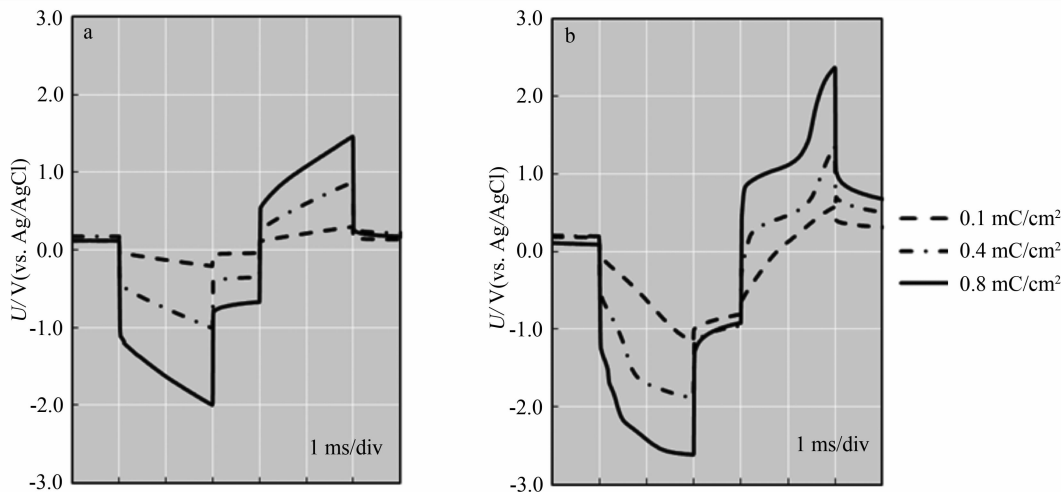

Fig. 5　The electroplated rough Pt electrode (a) presented lower and linear voltage excursion than that of the sputtered thin-film smooth Pt electrode (b) under the same pulse conditions

charge without generating irreversible electrochemical reactions. These electrodes must have low electrode impedance, high charge injection capability and high corrosion resistance[14,17].

　　Most devices use platinum, iridium oxide, or titanium nitride electrodes to inject the necessary current to elicit a neural response. These materials are chosen because of their ability to inject large amounts of charge with negligible electrode degradation[12,14,17]. To ensure longer device lifetimes, most devices incorporate electrodes with a large surface area and operate at well below the charge injection limit of the electrode material to avoid unnecessary dissolution and gas evolution, which could potentially damage biological cells.

3.4.1　Metal and Metal Oxide Electrodes

　　Platinum or platinum-iridium alloy is an electrode material widely used in neural stimulation. Its safe stimulation limit, defined by the amount of charge applied before hydrolysis and gas evolution, ranges from 0.1 to 0.35 mC/cm^2. For many stimulation applications that require a high density electrode array in a very small region, electrode size should be no larger than 100 μm in diameter[5]. The charge density required for effective stimulation with such small smooth Pt electrodes will be 0.35 ~ 1 mC/cm^2, which exceeds the safe stimulation limit. A new electrode material named "Platinum Gray" performs better than smooth solid Pt material and meets the requirement[18]. Platinum gray is similar to the more familiar platinum black except that it is prepared in a way to make it significantly more mechanically stable.

　　Compared to platinum, iridium can inject higher charge through oxidation reactions. The iridium surface is said to be "activated" through repeated voltage cycling which forms a thick layer of porous iridium oxide (IrO_x)[19]. Such porous three-dimensional bulk IrO_x material has a very high effective surface area and enhances charge injection capacity. As high as 25 mC/cm^2 charge capacity for IrO_x was measured in cyclic voltammetry. However, not all of this charge is available during neural stimulation due to slow mass transfer of oxygen in pores and slow oxidation-

state transitions[14]. For the short pulses used in neural stimulation, the practical charge-injection limit for iridium is less than 1 mC/cm^2.

　　Electrochemically activated IrO_x has been used as the electrode for intracortical stimulation of the visual cortex, for microphotodiode stimulation and for acute clinical trials in a retinal implant[5]. IrO_x coated Pt/Ir electrodes have been used in a commercial pacemaker for sensing and stimulation. Some studies indicate that chronic aggressive stimulation resulted in degradation of iridium and adverse tissue response. In order to fully utilize its high charge capacity, IrO_x electrodes need to be biased anodically[19].

3.4.2　Capacitive Electrodes

　　Electrodes that have a dielectric film such as Titanium nitride (TiN), TiO_2, Ta_2O_5, and $BaTiO_3$ are extensively studied materials for capacitive stimulation electrodes[19-20]. Among them, sputtered TiN appears to be the best dielectric material to use for stimulation and has a charge injection capacity similar to that of IrO_x. TiN is sputtered at high pressure in a nitrogen atmosphere to obtain a nanoporous surface. TiN has been used as a pacemaker electrode material clinically. Although the rough TiN provides a high interfacial capacitance, the maximum capacitance cannot be fully utilized at fast waveforms, due to the ohmic drop in the pore-like rough surface[21]. In an accelerated aging test, TiN electrodes were stable when subjected to gentle gassing by a cathodic voltage bias[5]. However, when the surface was subjected to a wider voltage bias and more vigorous gassing, there was damage to the TiN coating. In some cases, a total loss of charge-injection capacity was observed.

3.4.3　Conducting Polymers

　　Conducting polymers, Polypyrrole (PPy), polyaniline, and poly(3,4-ethylenedioxythiophene) (PEDOT), have been explored as new electrode materials for neural interfaces[16]. Conducting polymers offer some advantages over metal electrodes. They are unique materials, which have the ability to conduct electricity, but are organic in nature. In contrast to metal materials, soft conducting polymers may pro-

vide an improved bionic interface between the rigid e-lectronic devices and the soft, amorphous biological systems.

While conducting polymers hold much promise in biomedical applications, more research is needed to further understand the properties of these materials. Factors such as film stress, polymer volume changes and overoxidation under electrical stimulation, biocompatibility, and longterm stability are of significant importance and may pose challenges in the future success of conducting polymers in biomedical applications[16].

3.5　Microelectrode Arrays

There are mainly two types of electrode arrays used in biomedical implants; the planar type and the three dimensional needle/pillar type. For cortical and deep brain stimulations, needle-type electrode arrays are mostly used to reach target cells. A typical example for this type of electrode is the 100 silicon microelectrodes Utah array[10]. The electrode tip dissolution and array interconnection have prevented such silicon needle based arrays from long-term implantation. Needle-type electrode arrays, especially the high-density arrays, have been rarely used in retinal implants due to the possible damage of the retina by the electrode insertion. The protruding electrodes in a pillar-shaped gold electrode array implanted in suprachoroidal space were observed to cause some retinal layer detachment during retinal surgery[22].

Microfabrication processes have been used to make planar thin-film microelectrode arrays[23]. Planar electrode arrays are usually made from flexible polymers, such as silicone, polyimide, parylene, and polyurethane[5,8]. Silicone coated electrode arrays have been widely used in many commercial devices such as cochlear implants and spinal cord stimulators. The electrode arrays used in the early clinical studies in retinal implants are silicone-based flexible arrays. Figure 6 shows a fundus photograph of a silicone electrode array implanted in an eye. The electrode array was composed of 16 Pt disks (~ 500 μm in diameter) arranged in a 4 × 4 square array. The array was placed next to the retina and was curved to match the
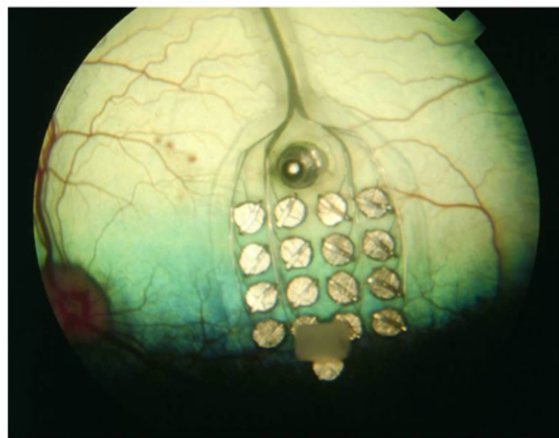

Fig. 6　A fundus photograph of a silicone electrode array inside an eye[5]

retina[5].

Smaller and thinner electrode arrays with flexible polymer substrates to follow the curvature of the implantation sites are the main trends in the development of micro-stimulating electrodes. Planar array configuration with a three-dimensional microelectrode structure to increase charge-injection capability has been explored (see Fig. 7)[24]. Using novel nanotechnology combined with well-established MEMS methods will produce batch-fabricated, low-cost electrodes for neural stimulation, recording, and chemical and biochemical sensing[25].

3.6　Cyclic Voltammetry in Characterizing Neural Electrodes

Electrochemical processes in neural stimulation include oxidation and reduction reactions. Water hydrolysis or gas evolution is the most common electrochemical reaction during pulse stimulation, which limits charge injection capacity of an electrode. Cyclic voltammetry (CV) has been used to study redox reactions and to define an operational potential window called a water window. The water window is the potential range between the hydrogen evolution or proton reduction to oxygen evolution or water oxidation[14,19,26]. The typical water window for a platinum electrode is − 0.6 V to 0.8 V determined by a slow CV in saline. CV also defines the electrode's charge delivery or storage capacity (CSC or Q_{cap}) in response to a slowly varying waveform , which repre-
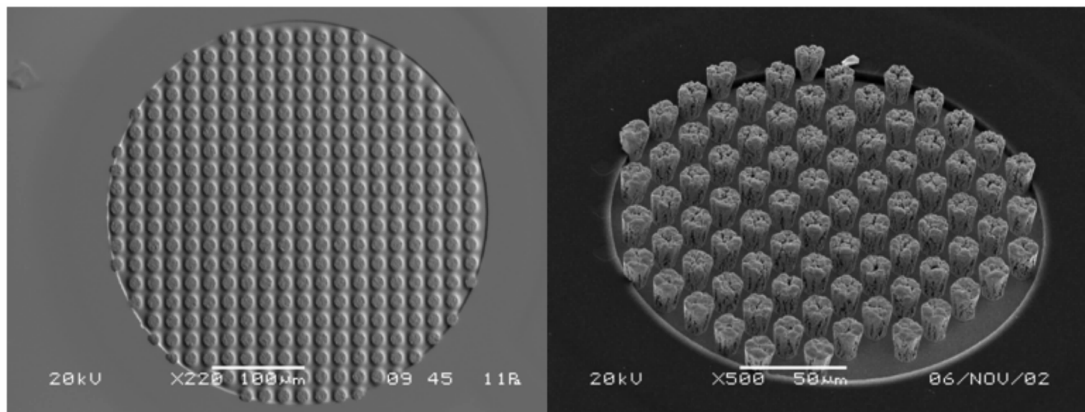
Fig. 7　SEM micrographs of planar electrodes with 3D microposts[25]

sents the maximum charge storage capacity of the electrodes. Experimentally, the Q_{cap} is estimated by integrating the area under the voltammogram within the water window.

In addition to determining the electrode reactions and charge storage capacity, CV can also reveal the stability of the electrode coatings. Figure 8 shows voltammogram changes recorded in a continuous CV on a PPy/NaDBS-coated Pt electrode[16]. As the number of CV cycles increased, the separation between redox peaks enlarged while the peak currents diminished. Larger peak separations suggest higher energy barriers required for oxidation and reduction reactions or poor reversibility. Lower peak currents indicate the reduction of electroactivity and loss of charge storage capacity.
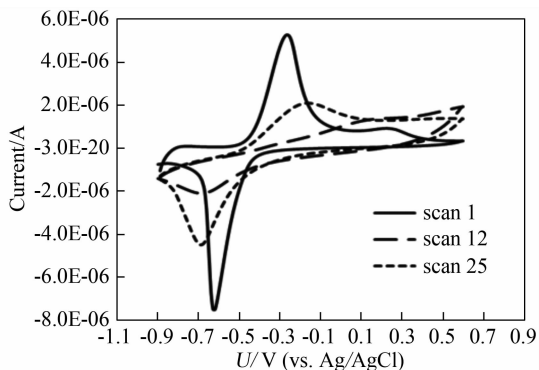

Fig. 8　Peak current and potential changes in voltammograms of a PPy/NaDBS-coated Pt electrode (voltammograms were recorded in PBS with a scan rate of 50 mV/s[16])

There are limitations in using CV to characterize stimulation electrodes. CV does not operate at the same time scales or voltage amplitudes as those used for neural stimulation; it may be inadequate for investigating true electrode dynamics[14]. Typical neural stimulation uses constant-current pulses of 10 ~ 100 μs in duration, where voltages often exceed 1 V on stimulation electrodes. In comparison, a typical CV has a sweep rate of 50 mV/s or ~1 min/cycle for a potential range from −0.6 V to +0.8 V, and thus is ineffective in reflecting the reaction kinetics of neural stimulation. CV at a faster sweep rate would be more appropriate for characterizing stimulation electrodes. However, at faster scan rates of 1 ~ 20 V/s, charging current from electrode capacitance dominates the total current response causing distortion of voltammograms. This makes it difficult to analyze these voltammograms in detail.

3.7　Electrode Impedance

Electrode impedance is related to the interfacial surface area between the electrode and electrolyte with impedance decreasing as surface area increases. As neural stimulation and neural response are high frequency in nature, impedance behavior at high frequencies is of particular interest for stimulation. Electrochemical impedance spectroscopy (EIS) has been used to characterize frequency response of stimulation electrodes. The small-signal perturbation used in the impedance measurements minimizes the oxidation and hydrolysis reactions. The electrode impedance is thus

dominated by the double-layer capacitance C_{dl}, which is in series with the electrolyte resistance R_s (see Fig. 3). At very high frequencies (> 10 kHz), the capacitor C_{dl} shunts all the current, and the resulting electrode impedance is approximately the electrolyte resistance R_s. In literature, the magnitude of impedance at 1 kHz, which is considered to be the clinically relevant frequency, is often reported as electrode impedance[16].

The capacitance of electrodes at a given frequency is determined from the imaginary component of the impedance[20]

$$C = 1/(2\pi f Z'') \tag{2}$$

where f is the frequency and Z'' is the imaginary part of the electrode impedance.

From Equation 2, it is clear that the measured double layer capacitance is frequency dependent and it decreases with increasing frequency. Low capacitance at higher frequencies will result in a low injectable charge capacity for pulse stimulation which usually employs fast varying waveforms. The electrode capacitance at 1 kHz can be used to compare charge delivery capacity and electrode surface roughness.

EIS is a more convenient method for evaluating electrodes than that of CV. In a single EIS measurement, the frequency dependence of electrode impedance can be determined. The electrode resistance and capacitance are easily separated. However, the small potential (~ 10 mV) without DC bias used in EIS does not accurately reflect the performance at high potentials that are involved in oxidation or reduction reactions.

3.8　Biocompatibility and Biostability

Chronic neural stimulation requires charge injection through electrode/tissue interface at a high frequency for a prolonged period of time. This poses unique challenges to metals, metal alloys and surface coating materials used as neural stimulation electrodes. To provide adequate safety in implantable medical devices, tissue-contacting materials including electrodes and insulation materials need to be biocompatible and biostable. Biocompatibility ensures that the tissue being stimulated is not damaged while bio-

stability ensures the stimulating electrode itself is not damaged due to corrosion or degradation. For chronic stimulation applications, it is critical that these properties are stable for a prolonged period of time to achieve long-term quality performance[27].

When an electrode is implanted into the body, the implant surface will be in contact with blood, proteins, cells, etc. It then mediates cellular responses. Blood platelets will then actively promote blood clotting and release growth factors to enable cell adhesion and proliferation, tissue growth and finally fibrous tissue encapsulation of the implant materials. Some foreign body reactions or host responses to implants involve the adhesion and activation of monocyte/macrophages on the device surface and production of oxygen free radicals. Hydrogen peroxide is also produced by macrophages and can permeate the material. Some earlier pacemaker electrodes suffered so-called environmental stress cracking due to surface oxidation in the body[27]. Incorporating some anti-inflammatory drugs either through a surface coating or through embedded microfluidic drug delivery channels in the implant has reported to be effective to reduce inflammation at the electrode-tissue interface of cardiac pacemakers and control fibrous capsule formation[23].

To introduce a new material for use in an implantable device, international guidelines and standards such as ISO 14971: "Application of Risk Management to Medical Devices" and ISO 10993-1: "Evaluation of Medical Devices" need to be followed. Since the in-vivo environment and complicated in-vivo host reactions towards implants cannot be duplicated in-vitro, some biodegradation processes are hard to reproduce in testing labs. A series of in-vitro and in-vivo tests may qualify a material for implant. However, the long-term performance of the material needs to be continually monitored through post market surveillance[1,27].

3.9　Neural Electrode Failures

Severe electrode failure including corrosion, oxidation and delamination during clinic application will cause tissue damage and reduce the lifetime of such medical devices. The effects of various pulse stimula-

tion conditions applied on the Pt micro-electrodes were studied in order to optimize the stimulation protocol for clinic applications and to predict possible failure modes when a given stimulation protocol was used[28]. Results show that at charge density higher than $0.1 \sim 0.35$ mC/cm^2, smooth Pt electrodes presented clear surface corrosion associated with metal dissolution, dissolution-deposition and/or surface layer build-ups depending on pulse and stimulator conditions.

Pt dissolution in saline involves Pt ions complexing with chloride. Some dissolved Pt ions accumulated in the vicinity of the electrode surface. Such dissolved Pt ions during the anodic phase of a biphasic pulse were electro-deposited back to the electrode surface when the current reversed to the cathodic phase. This dissolution-deposition process caused surface morphology change and was observed to reduce electrode impedance initially due to increased surface roughness. However, it is detrimental to electrode lifetime, especially to thin-film electrodes as it may cause structure damage.

In most DC experiments conducted in diluted sulfuric acid, Pt is said to have only a mono layer oxide buildup. When used in pulse stimulation conditions, high frequency pulses have been observed to cause thick oxide build up on Pt electrode surfaces. The Pt oxide layer displayed higher impedance and caused surface expansion, cracking and eventually

delamination (see Fig. 9). More studies are needed to fully understand the electrode reactions under high frequency pulse stimulation in saline[26,29].

Since the corrosion and oxidation are anodic processes, an electrode is more susceptible to failure when positively biased. Study indicated that a charge-imbalanced waveform with a slight cathodic bias had the "cathodic protection" effect to minimize Pt corrosion and oxidation due to reduced positive potential during the anodic phase and during the interpulse interval between pulses[12,14,30]. However, the cathodic bias scheme poses a challenge on the circuit design of an implantable stimulator.

For surface-modified electrodes, the physical degradation, including cracks and delamination, has been observed as the major mode of failure in long-term stimulation[16]. In a study of PEDOT and PPy coating on Pt electrodes, the thickness of the PEDOT coating showed direct effect on the mechanical failure observed. It was found that thicker films, although they have lower impedance and higher charge capacity, showed more mechanical failures such as cracking and delamination under chronic stimulation, possibly due to the higher stress imposed on the film[31]. Thinner films have better adhesion and appear physically stable. However, the charge capacity is not enough to handle stimulation charge density higher than 1 mC/cm^2.
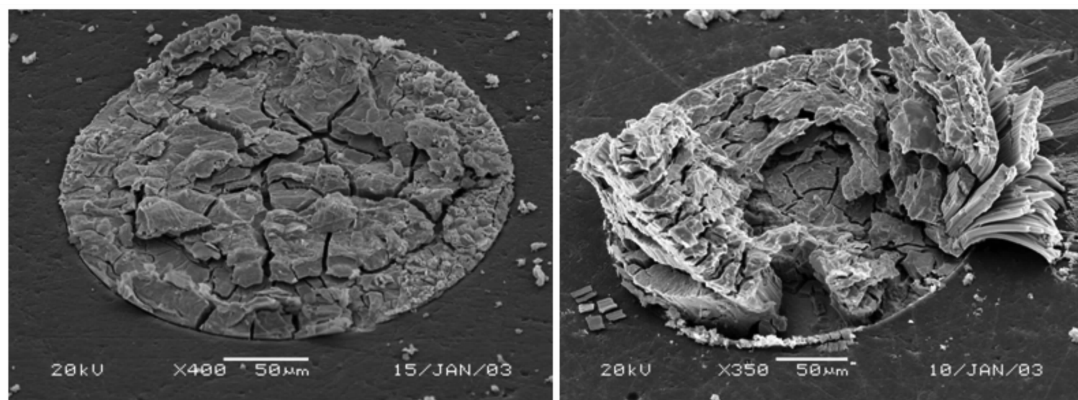
Efforts have been made to improve the adhesion

Fig. 9　Pt oxide layer formed under some neural stimulation conditions which causes surface layer expansion and induces cracks[28]

of conducting polymer to metal substrates. One strategy is to covalently attach the polymer to the electrode surface. Another, more effective approach is roughening the surface of the metal substrates by electroplating or chemical etching. In a recent study, carbon nanotubes (CNTs) doped PEDOT has shown both increased stability and charge injection capacity[32].

4　Microsensors and Microbiosensors in Biomedical Implants

Most implants are only used for stimulation and no sensor feedback control functions are implemented. Medical devices with integrated sensor systems may permit early corrective therapy or provide feedback in order to control the devices to form so called "smart" closed-loop controlled medical implants[25]. Some examples of sensors needed for visual implants are chemical sensors such as pH sensors and ion selective electrodes, some gas sensors for oxygen, hydrogen and chlorine, impedance/voltage sensors, and biosensors, such as glucose, ascorbate, lactate and glutamate sensors.

Glucose detection inside the eye is potentially important for the development of retinal implants. The nutritional supplies for the retina, including glucose, are provided by both choroidal and the retinal circulation. An exceptionally high rate of glucose metabolism inside the retina was reported and this may be the cause for lower glucose concentration in the vitreous humor than that in plasma[33]. A clinical study suggested that chronic implantation of retinal arrays likely obstructed the nourishment to the retina and caused both inner and outer retina damage[34]. Closely monitoring the glucose concentration changes during retinal stimulation and array implantation will reveal such blockage of nourishment.

Glutamate is the main excitatory neurotransmitter in the central nervous system, and plays an important role in neurodevelopment and neurodegenerative disorders during aging. Studies on neural stimulation have established the link between the activation of neurons and the release of L-glutamate, a neurotransmitter in the retina[33]. Multi-analyte biosensors may be also desirable to be integrated with visual implants to detect simultaneously multi-analyte changes such as glucose metabolization processes to form lactate in the retina.

Numerous publications have appeared about different biosensors, the majority of which are glucose oxidase based enzyme biosensors. However, a survey of this literature shows that only a limited number of these devices have been applied to real samples, and very few are commercially available[35].

Almost all faradaic reactions produce or consume hydrogen or hydroxyl ions. Since the presence of these ions at the electrode surface alters hydrogen ion concentration, one can expect a stimulus induced pH shift[25,36]. The changes in pH can have a significant effect on the electrode/electrolyte interface. Shifted pH will change the electrode's corrosion potential and cause electrode materials to dissolve. Large pH changes also affect cell function, altering the structure and activity of proteins, ionic conductance of the neural membrane, neuronal excitability and even causing tissue damage[37].

Previous studies from cochlear and retinal implants research show that the extent of pH changes is related to stimulus rate, intensity and the residual direct current levels[36]. A planar thin-film micro-pH electrode based on IrO_x arrays has been developed to detect stimulus induced pH in the electrode/tissue interface[37]. The pH changes due to electric stimulation were recorded successfully by the planar micro pH electrode array in-vitro (see Fig. 10a). A two dimensional distribution of pH change was established by using such combined microelectrode arrays (see Fig. 10b).

While many challenges exist in the development of implantable sensors, major hurdles include biocompatibility, sensor packages, chronic stability and in-vivo calibration[25,35,37]. Microsensors and microbiosensors developed thus far are not specifically designed for medical implants. The sensors developed for the retinal prosthesis should be preferable in micron or sub-micron scales due to the limited space on implants and should be suitable for acute or chronic
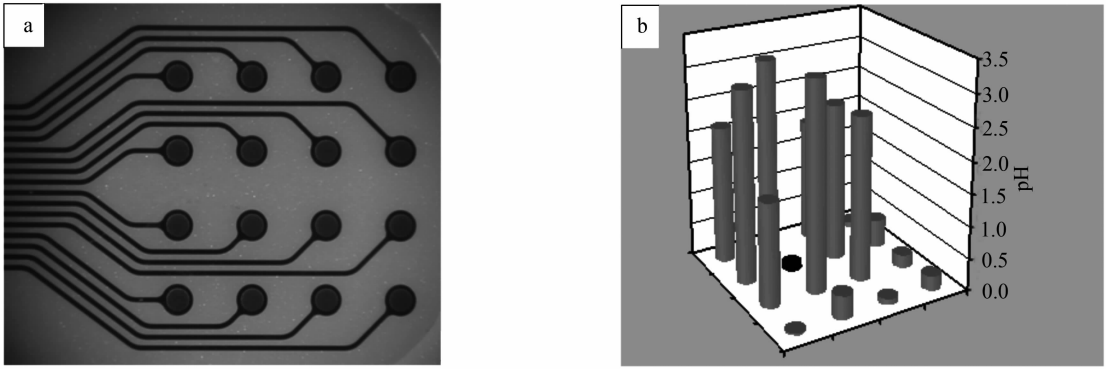
Fig. 10　An IrO$_x$ based planar micro-pH electrode array(a) and two-dimensional pH distribution measured after stimulation for only one minute(b) the electrode site in dark color is the Pt stimulating electrode, all other 15 electrodes are iridium oxide pH sensing electrodes[37]

implantation.

5　Conclusions

Advances in biomedical engineering, micro-fabrication technology, and neuroscience have led to many improved medical device designs and novel functions. However, many challenges remain. This paper reviewed electrochemical aspects of implantable medical devices and highlighted the designs and technical challenges of medical implants from an engineering perspective. Most topics reviewed in this paper are from a two-volume book serial titled `Implantable Neural Prostheses´ published by Springer in 2009 and 2010. We hope a better understanding of design issues, techniques, and challenges may encourage innovation and interdisciplinary efforts, especially from electrochemists to expand the frontiers of R&D of biomedical implants.

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与生物医学植入器件中的神经电刺激过程
相关的电化学研究

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摘要： 生物医学工程、微电子加工技术和神经科学的进展推动了用于神经电刺激的新型和先进的生物医学器件的问世，使各类患者的某些感官功能得以恢复，并改善了患者的生活质量. 在这些生物医学器件中，人工耳蜗植入器件、人工视觉植入器件、深层脑部刺激器件和脊髓刺激器件都取得了很大进展. 刺激电极是生物医学植入器件中的关键部件之一. 当刺激电极与活体组织相接触时，形成了电子器件和生物体组织间的接触界面. 本文首先以耳蜗植入器件和视觉植入器件为例，简要介绍了生物医学植入器件的工作原理和现状. 在此基础上，着重对神经电刺激器件所涉及的电化学概念、测试方法及其进展进行了评述. 介绍了电刺激和电极/活体组织界面上电荷注入的基本原理和机制. 也对常用的电极材料和微电极加工技术进行了评介. 讨论了植入式器件研发过程中所遇到的与电化学相关的挑战，诸如电极反应、电极阻抗、电荷注入容量、微电极阵列、电极腐蚀以及生物兼容性等. 此外，也讨论了微型传感器和微型生物传感器在植入式器件中的应用前景. 刺激电极长期处于活体组织内的苛刻条件下会渐渐失效，腐蚀、氧化和脱壳等情况的出现都会降低器件的使用寿命，甚至危及机体. 本文也对此进行了讨论. 对设计和加工所面临挑战的清醒认识促使包括电化学家在内的多学科专家和工程技术人员共同努力，以推进神经刺激生物医学植入器件的长足进展和实际应用，使感官功能失效的患者得以受惠.

关键词： 神经刺激；生物医学植入器件；电极/活体组织界面