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Implantable Electrodes with Carbon Nanotube Coatings

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1. Introduction

Carbon nanotubes (CNTs), discovered in 1950 (Monthioux & Kuznetsov, 2006; Radushkevich & Luk'yanovich 1952) and rediscovered in 1993 (Iijima & Ichihashi, 1993), came into the limelight as a promising next generation material for standard electronics, computers and aerospace industries. Its ballistic conductance, chemically inert nature (Niyogi et al., 2002), nano size (Ajayan 1999) and ease of chemical functionalization (Shim et al., 2002; Sinnott, 2002) opened the doors for it to become an important biomaterial (Malarkey & Parpura, 2007). The diameter of the nanotubes is of particular interest to neuroscientists: they are of the same order as neuronal processes. The interface of sub-cellular compartments with a material of that same size spawns numerous new ideas. This facilitates an interaction at a molecular level, imperative in the formation of "functional neuronal circuits"(Lee & Parpura, 2009), was one of the possibilities considered early on. CNTs could be functionalized with one or more bioactive molecules (Mattson et al., 2000). The molecular control of neuronal architecture at focal microdomains seemed possible now. This promoted the candidacy of CNTs out of the variety of available nanomaterials, and onto the main neuroscience stage (Pancrazio, 2008).

In this chapter we will discuss the use of CNTs as active coatings for implantable neural electrodes (NEs). We begin with the background and motivation behind NEs, discussing a few examples of electrical stimulation and recording used in treating or ameliorating various nervous disorders. There are various techniques for the evaluation of electrode performance. The two most important are cyclic voltammetry and electrochemical impedance spectroscopy. These techniques are the focus of a section which includes robustness and reliability in neural electrodes. The rationale behind using CNT as a NE coating is discussed next. It throws light on the properties that make them unique. We describe the figures of merit of CNTs with respect to the development and requirements necessary for designing stimulating electrodes. The problems associated with using CNTs fabrication and manipulation are also discussed with the objective of establishing an appropriate view of the challenges faced when using and handling this material. A discussion on CNTs and neuronal interactions then follows. We will limit our approach to a subset of studies relevant to using CNTs as a conductive substrate to stimulate and record

from neuronal cell lines, which we call "neurocompatibilty". Various techniques have been devised to deposit CNTs on substrates for biological interaction. The following section consists of methods mentioned in the literature to deposit CNTs specifically as an electrically active neural interface and characterization results. This is followed by overview of *in vivo* studies conducted using CNTs as electrodes to stimulate and record from the nervous system. We will conclude this chapter with the current limitations and future investigations of CNTs as NEs.

2. Background and motivation

Luigi Galvani was a pioneering scientist who opened the doorway of using electrical stimulation on excitable tissue. He showed, in his famous experiment in 1780 on a frog, that muscle could contract as a result of electrical stimulation. This work led Galvani to propose that electricity is secreted in the brain and thus distributes itself from nerves to muscles (Parent, 2004). His work paved the way for the development of modern electrophysiology. His nephew Aldini, in 1803, at the Royal College of Surgeons, applied an electric shock to the corpse of a criminal. The results were theatrical. In his own words "when the rods were applied to Foster's mouth and ear, the jaw began to quiver, the adjoining muscles were horribly contorted, and the left eye actually opened" (Parent, 2004)**.** This famous experiment led to the idea that electricity can restore life; from then on neural and muscular tissues became the focus of research on controllable electrical stimuli to induce activity. Technological advancements such as, cathode ray oscilloscope, micro-wires, and galvanometer later in the 19th and 20th centuries helped in understanding the structure and functions of excitable tissues such as neuronal and skeletal, cardiac, and smooth muscles. Nowadays long-term electrical stimulation is used to treat different neurological and muscular disorders(Bhatt, 2001). From the 20th century on neurologists have been using electrical stimulation to identify specific sites in the brain. Today electrical stimulation of relevant brain regions to alleviate symptoms of certain neurological disorders is available clinically.

Electrical stimulation is used to treat various kinds of disorders, from pacing the heart (through pacemakers) to bladder control. Electrical stimulation is delivered to its targets through electrodes. Here we will focus on electrical stimulation of the nervous system, more specifically of the central nervous system. With the exception of transcranial direct stimulation, applied from outside the skull (a non-invasive technique), electrical stimulation of the nervous system requires implantable electrodes. We focus here on those applications: brain stimulation by means of electricity delivered via microwires or microelectrodes that are inserted in the brain.

One of the popular treatments of Parkinson's disease is deep brain stimulation (DBS), where microelectrodes are placed in regions of the brain called thalamus, sub-thalamic nucleus, and globus pallidus (Vitek, 2002). Electric stimulation is applied to prevent tremor and other involuntary movements. The exact mechanisms of deep brain stimulation are still not clear, although there are many models proposing sometimes controversial mechanisms of action (Vitek, 2002). In order to restore functional vision, microelectrode arrays have been implanted over the visual cortex (Wyatt & Rizzo, 1996). Cochlear implants also use microelectrodes that restore hearing of patients by

stimulating specific regions of the auditory nerve (Wilson et al., 1991). Lastly, electrical stimulation is used to treat neurological disorders such as drug resistant depression (Mayberg et al., 2005), Tourette's syndrome (Servello et al., 2008), and epilepsy (Velasco et al., 1995).

Neural recordings are helpful in at least two applications: brain-computer interfaces and rehabilitation. For example, patients with movement disorders due to the failure in the connection between the cerebral motor system and muscles caused by injury, stroke, or degenerative disorders could benefit from recording electrodes. This missing or damaged links can be restored by recording the intent from the cerebral motor system and using those signals to control a prosthetic device. On another application, recording electrodes may also help deciding on stimulation protocols for an already implanted DBS electrode system. This will be highly beneficial when developing an adaptive and patient-tailored, closed loop system.

2.1 Invasive electrical interfacing with body

There are invasive and non-invasive methods for electrical stimulation and recording. An ideal invasive electrode used for stimulation or recording should be small, so that there is minimal tissue damage, and it should have enough recording sites for monitoring many neurons simultaneously. These electrodes can be made of various metal substrates such as platinum or medical grade stainless steel.

The electrode is the interface between the body and the prosthetic device used for electrophysiological research. One side is the metal electrode attached to an electrical circuit: here electrons are the charge carriers. The second side is the physiological medium (electrolyte) where charge is carried by ions. The fundamental process occurring at the electrode-electrolyte interface is charge transduction between electrons of the metallic electrode and ions of the electrolytic species. The two basic mechanisms of charge transfer at the electrode-electrolyte interface are faradaic and non-faradaic, as briefly discussed below. For more detailed descriptions of types of electrodes, we refer the reader to electrochemical textbooks (Bard & Faulkner, 2006; Varma & Selman, 1991).

2.1.1 Faradaic charge transfer

Here reduction and oxidation of chemical species in the electrolyte take place during electron transfer to and from the electrode. During reduction an electron is added to the chemical species and this occurs when the electrode is driven to negative potentials. In oxidation, removal of an electron from the chemical species occurs when the electrode is driven to a positive potential in reference to the solution (figure 1). This mechanism injects redox products in solution. In a reversible charge transfer the redox species injected into the electrolytic media are recovered at the electrode surface when the direction of current is reversed. A typical example of a Faradaic charge transfer is the process at the surface of silver-silver chloride electrodes.

2.1.2 Non-faradaic charge transfer

Charge redistribution can also occur by charging and discharging of the double layer present at the electrode-electrolyte interface. The double layer acts like a capacitor, with the

metallic electrode as one plate and the other being the electrolyte/tissue (Guyton & Hambrecht, 1974). Ions from the electrolyte either move towards or away from electrode depending on its charge. This process doesn't involve actual electron transfer between the electrode and the electrolytic species.
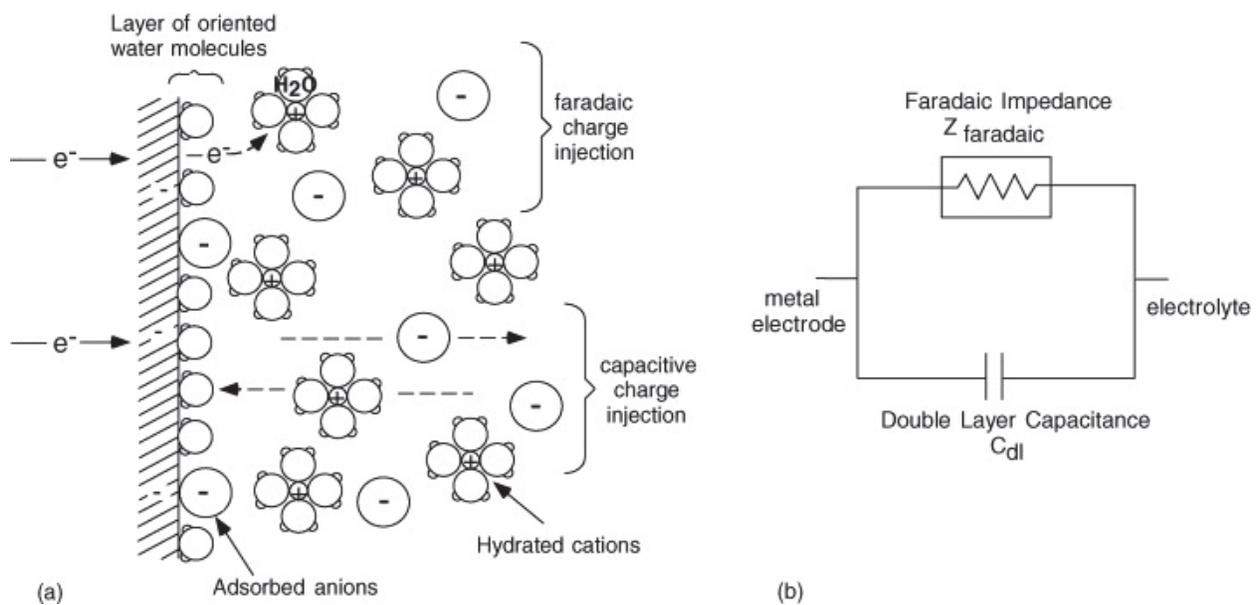
Fig. 1. Schematic of faradaic and non-faradaic (capacitive) charge transfer at the electrode-electrolyte interface. Reprinted with permission from (Merrill et al., 2005) . Copyright (2005) Elsevier.

Usually, the charge presented by a conventional metallic electrode through a stimulus pulse is above the holding capacity of the double layer. Thus, the charge transfer contribution of the electrochemical faradaic mechanism dominates the capacitive non-faradaic mechanism (Guyton & Hambrecht, 1974).

3. Electrode characterization

Electrode characterization is carried out in order to understand the nature of the electrode performance when it is exposed to biological tissue. Properties of particular interest are the charge injection level, electrochemical and structural properties, corrosion levels, and the potential window. There are various techniques involved in measuring or characterizing each of these. For example, structural characterization can be done using scanning electron microscopy (SEM), tunneling electron microscopy, and atomic force microscopy to study the surface morphology of the electrode. Similarly, there are various methods for electrochemical characterization. In controlled current methods a constant current is passed between a pair of electrodes in an electrochemical cell and the voltage of the working electrode is measured at the same time (Sawyer & Roberts, 1974a). There are various types of control potential methods: chronopotentiometry, chronoamperometry, and chronocoulometry. In controlled potential methods the voltage between the electrodes is kept constant and the current flowing in the electrochemical cell is monitored (Sawyer & Roberts, 1974b). Controlled potential coulometry techniques, linear sweep and cyclic

voltammetry (CV) experiments are a few examples of controlled potential methods. Controlled current methods are used evaluate the diffusion coefficients, rates of electrode processes, adsorption parameters, and rates of coupled chemical reactions occurring at the electrode surface within the supporting electrolyte (Sawyer & Roberts, 1974a). Linear sweep voltammetry evaluates the mechanism, kinetics and thermodynamics of the chemical reactions. Cyclic voltammetry (CV) is a derivative of linear sweep voltammetry, which captures both the oxidation and reduction cycle of the system. The last method we will discuss is electrochemical impedance spectroscopy (EIS), which investigates the interfacial reaction mechanisms and is essential to evaluate depositions (Macdonald, 1991). There are many other techniques described in detail in the literature (Bard & Faulkner, 2006; Varma & Selman, 1991).

3.1 Electrochemical characterization
The most important methods for biological electrodes are CV and EIS. CV measures the maximum charge that the electrode can deliver. This information is essential in evaluating electrodes used for electrical stimulation of tissue. EIS not only shows the voltage-current behavior of the electrode in the electrolyte but it provides information on the way the impedance of an electrode varies for a chosen frequency range. This data is essential because both high and low frequency stimulation of tissue are performed to study and treat various disorders. The two methods, CV and EIS, are discussed below.

3.1.1 Cylic voltammetry
CV is an electrochemical method where the potential of a working electrode is varied with time in a triangular waveform (figure 2). The current through the electrochemical cell is measured during the complete cycle of forward and reverse sweep rates (Crow, 1994). The potential is varied at sweep rate ranging from 10 mV/s to about 1000 V/s and the respective current is recorded as a function of potential. While the potential is varied, the surface of the electrode becomes sufficiently negative or positive,a solution species may gain or transfer electrons to and fro from the electrode surface. This movement of electrons generates current in the electrode circuitry. The reaction at the electrode surface varies from reduction, oxidation or none (Evans et al., 1983) and depends on the electrode potential. In a completely reversible system, species reduced in the forward scan of each cycle are re-oxidized during the reverse scan.
CV is useful in chemical research that provides an interpretable format regarding the electrochemical processes characterizing the electrode-electrolyte interface. (Sawyer & Roberts, 1974b). The integrated area of the CV of any electrode is equal to its charge storage capacity (CSC). To understand the curve, first assume that the electrolyte contains a species O; R is its reduced form and its reducing potential is E0. Initially, non faradaic currents will flow as the electrode potential is greater than the reduction potential. As the electrode potential approaches its reducing potential, reduction begins and the faradaic current is established. When the electrode potential crosses the reducing potential, most of the O species is reduced to R. As the potential is reversed and crosses the reducing potential most of the R species oxidized to O and anodic current flows. As the surface concentration decreases, a limit sets on oxidation and reduction of the electrolytic species, followed by the depletion effect (Bard & Faulkner, 2006). This shows up as the oxidation (Op) and reduction peaks (Rp) (figure 2C).
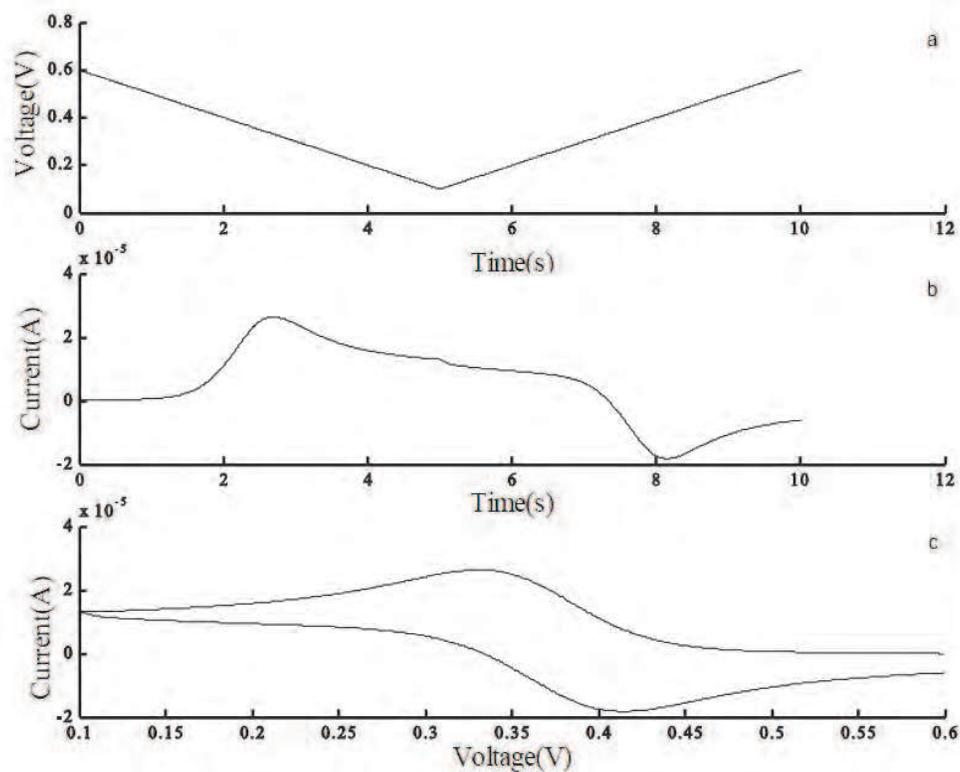
Fig. 2. (A) Applied voltage, (B) Measured current, (C) CV, combining (A) and (B).

3.1.2 Electrochemical impedance spectroscopy

The current-voltage behavior at the interface due to faradaic, non-faradaic and electronic components is described by impedance (Stieglitz, 2004) , measured through EIS. In this technique the system response is measured for a small amplitude, periodic AC signal spanned across a range of frequencies (Lasia, 1999). As the input and output signals are alternating current (AC) the impedance measure is complex. The real part is resistive and the imaginary part is the capacitive nature of the electrode. Nyquist and Bode plots are common graphical representations of complex impedance.

4. Requirements for successful neural electrodes

As in any engineering project, the design of robust electrodes for implantation entails careful analysis. The requirements should be stated with the goal in mind of a successful ten or twenty year lifetime: electrodes need to be functional during that whole period, either as recording or as stimulating devices. This is no easy task: mechanical, electrical, and biochemical constraints come into play (Merrill et al., 2005). A short description on the requirements for a neural electrode (NE) with a brief discussion of each figure of merit from the perspective of CNT electrodes follows.

4.1 The importance of impedance

Implanting an electrode in the brain wounds nearby tissue by severing capillaries, thus causing anoxia, and consequentially also neuronal and glial death (Perry 1994; Polikov et al., 2005). This trauma activates cellular mechanisms that aim at maintaining homeostasis

(Anderson, 2004). The insertion damage activates central nervous system macrophages which immediately secrete members of IL-1 (interleukin-1) family and other pro-inflammatory cytokines and chemokines. These in turn promote astrogliosis (Perry, 1994). Astrogliosis leads to reactive glial scar tissue formation, which has been shown, through histopathological techniques, to extend over weeks to years (Griffith & Humphrey 2006; Polikov et al., 2005). The reactive gliosis creates an insulating layer around the electrode, thus increasing the apparent impedance to the tissue. The take home message, from an inflammatory perspective, is that inserting a foreign body into the brain has multiple consequences, one of which is the formation of a shield around it. This is relevant in the design of an implantable electrode because an insulating layer around an electrode would mean no passage of direct current between the conductive material and the biological tissue. The main target for a NE, as the name indicates, are neurons. Spatial proximity to neurons determines how well the signal is transferred. The common analogy that helps visualize the relevance of this spatial variable is a microphone in a football stadium: if a reporter is interviewing a player after a game, and the microphone is next to his mouth, one can hear his comments. Were that microphone five feet away, we would hear the roar from the audience, and if he screamed we could tell whether he was speaking or not, but we could never hear the words out of his mouth. When recording from neurons in the brain, the cells immediately around the electrode will be heard (recorded from) loud and clear. If there is a "space" (either physical space or an insulating layer) between the electrode and the cell, we lose signal. This would decrease their efficiency in recording low voltages and would require higher voltages/current to deliver the same amount of charge for stimulation. This would be harmful to the tissue. Thus electrodes having lower impedance can compensate for the rise in impedance *in vivo*.

CNT walls consist of hexagonal network of carbon atoms that are sp2 bonded. The electrons thus are delocalized and mobile inside and outside the nanotube channel. This renders them with a high electrical conductivity, on the order of 10^8 $\Omega^{-1}m^{-1}$ (Baxendale, 2003). Coatings of functionalized and non-functionalized CNTs decrease the apparent electrode impedance measured. Thus a high signal-to-noise ratio (SNR) can be maintained while measuring small (micro Volts) neuronal signals from the extracellular space.

4.2 Mechanical integrity

The electrode material should maintain its mechanical integrity, which means that the material should not bend, delaminate, or break when passing through tissue. It should withstand movement between the electrode and the tissue after implantation. The material should not degrade if placed in an electrolyte medium for extended periods, under physiological conditions. CNTs are known to be one of the strongest materials that can be manufactured, with a Young's modulus of a single carbon nanotube exceeding 1TPa, about five times stronger than steel (Treacy et al., 1996). Despite this fact, CNTs are very flexible. Molecular dynamic techniques have helped to demonstrate that nanotubes restore back to their formal shape on removal of mechanical stress (Salvetat et al., 1999). This shows that CNTs are mechanically strong as well as flexible. This property of high strength and flexibility is essential in the design of penetrating electrodes. Compromises must be met however if the CNT is used merely as the last coating on a substrate: the mechanical characteristics of the substrate will obviously influence the integrity of the electrode.

4.3 Charge delivery and electrical stability

An electrode should be able to deliver sufficient charge through the double layer formed at the electrode-tissue interface to elicit an action potential. The charge delivered should be at a low electrode potential to prevent water electrolysis and damage the tissue. For any electrode there is a reversible charge injection limit i.e., the total amount of charge that an electrode can deliver before the electrode potential reaches the water electrolysis potential. Therefore, the reversible CSC of an electrode material should be high enough to deliver sufficient charge before irreversible reactions initiate. The reversible CSC depends upon the electrode material, electrolytic species, and on the stimulation parameters. Even if the electrode material is biocompatible the faradaic reaction byproducts must not be toxic to the tissue. Also these redox byproducts should not cause damage to the electrode itself.

The entangled matrix of CNTs over a substrate and the hollow inner channel of a nanotube help in transportation of ions but also enhances the double layer effects (Fang et al., 2006). This is helpful because by increasing the effective area or accessible layer that contributes to double layer we can deliver the required amount of charge by keeping the size of the electrode small, a necessity of biological electrodes. Such bioelectrodes have large surface area making CNTs ideal materials even for energy storage (Du & Pan, 2006). Research has shown that charge transfer of pure CNT in an electrolytic medium is mostly non-Faradaic (Barisci et al., 2000). This type of charge transfer doesn't allow the formation of oxidation and reduction species. CNTs are often functionalised and co-deposited with other materials over electrodes. This could induce redox reactions and thus may lead to faradaic charge transfer (Barisci et al., 2000).

Neurons and electrically excitable cells have been successfully recorded from and stimulated via CNT substrates. CNT-neuronal interaction has resulted in enhanced efficiency in signal transmission (Mazzatenta et al., 2007), efficient stimulation (Gheith et al., 2006; Liopo et al., 2006; Lovat et al., 2005) , and recordings with high SNR (Keefer et al., 2008).

4.4 Water window

The potential window is defined as the voltage range above which irreversible electrochemical reactions take place. This is commonly used to evaluate the quality of the electrode material. One could test electrode materials in any solution of interest. However, in the case of a biological electrode the working potential window should be well within the water window limits. The reason for that is the presence of water in biological tissue. A water window is defined as the potential region between the oxidation of water to form oxygen and the reduction of water to form hydrogen.

Due to its "well defined graphitic structure" , CNTs have a wide working potential (Hue et al., 2004) making it possible to work well within the water window limit. Figure 3 shows electrodes being cycled in phosphate buffered saline, inside and outside of the water window. The extremely high currents are indicative of irreversible reactions taking place at the interface.

4.5 Surface topography

Surface topography can influence the growth and orientation of neurons in culture. Surfaces having nanofeatures have been shown to influence cell attachment and can be used to navigate cells to a specific region on the silicon substrate. (Craighead et al., 1998). CNT electrodes can be used to position and form stable networks due to the stable and strong

physical interactions between the neurons and the CNTs. (Sorkin et al., 2009). The neurons move towards CNT covered surfaces and single neurons move particularly towards the CNT surfaces (Galvan-Garcia et al., 2007).
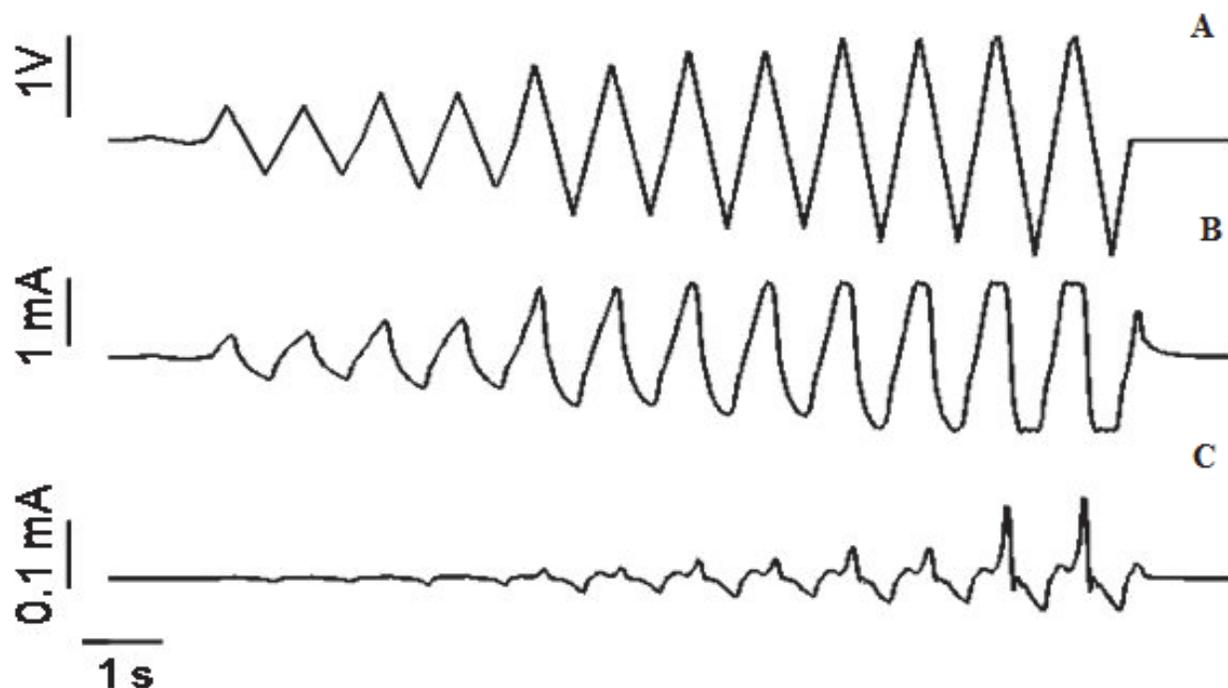
Fig. 3. Voltage controlled stimulation can drive electrodes outside the safe region determined by the water window. Stimulation sequence with 1 Hz triangular waveform, two periods per setting; amplitude of stimulus increases from 0.5 V to 0.7 V, then 1.1; 1.3; 1.5; 1.7 V. (A) Stimulation voltage, measured versus silver/silver chloride pellet in solution. (B) Current through iridium oxide film electrode, with 1 mA scale. During the 1.7 V peak stimulation, current through the iridium oxide is clipped due to amplifier saturation (amplitude higher than 1 mA). (C) Current through MWCNT electrode. Scale bar is 100 µA. Oxidation peaks are typical of non-reversible reactions at the electrode surface.

4.6 Biocompatibilty

The electrode surface, which contacts the biological tissue, should be biocompatible. Biocompatible means that the material will not induce toxic effects once in contact with the body. Another important quality of the material should be to not cause excessive immune response. Once an electrode is implanted it will be treated as a foreign material by the body, but the material should not impact the immune system dramatically (Polikov et al., 2005). This kind of response would reduce the electrode charge delivery capacity and recording sensitivity (Williams et al., 2007). Biocompatibility of CNTs is highly dependent on their mode of production, size, purification chemical functionalization, dose, and type of administration (systemic etc) (Ciofani et al., 2010; Nayagam et al., 2011). However, CNT surfaces are chemically inert (Niyogi et al., 2002) and can be modified by various functional groups to tailor them for a specific biological function.

As a substrate for neural implants CNTs seem to be bio- and neuro-compatible (see section 5 of this chapter) as they allow for neuronal growth and differentiation. CNTs as substrates for neuronal growth were first explored by Mattson et al in 2000. Since then studies on neuronal growth and interactions with CNTs have increased tremendously. CNTs tend to create an effective anchoring site for neurons and glial cell differentiation (Jang et al., 2010; Sorkin et al., 2009).

CNT coated surfaces are neuro-adhesive in *in vitro* scenarios (Galvan-Garcia et al., 2007). We believe this is an indication of a more generalized, also *in vivo,* behavior: certain kinds of CNT perform well when implanted in any excitable tissue. For example, immobilized multi-walled-walled CNT (MWCNT) arrays were implanted in male guinea pig muscles (Nayagam et al., 2011). The immobile CNTs presented with an insignificant host response while the dislodged CNTs were phagocytosed. The CNT arrays showed a minimal level of surface fouling. These results are very encouraging for further developing neural electrodes.

4.7 Issues associated with CNTs as neural electrodes

Although CNTs are promising, there are limiting factors when using it as electrode material for biological purposes. Pristine CNTs are inherently hydrophobic materials (Yang et al., 2007). Their surface are made of non-polar graphitic basal plane and hence most of this high surface area doesn't contribute to charge transfer in an aqueous media (Wang et al., 2006). Hence, surface modification of nanotubes is imperative to make them hydrophilic (Lacerda et al., 2006). Organic solvents render CNT surfaces hydrophilic and thus are used as a treatment technique. These solvents might be trapped between porous nanotubes or inside them even after extensive treatment for solvent removal (Wang et al., 2006).

The bioavailabilty of metallic catalysts used to grow CNTs might also contribute to harm the tissue (Guo et al., 2007). Thus harsh purification methods need to be employed to remove metal catalysts (Fe, Ni) (Hu et al., 2003). The current techniques of making CNTs are limited in the sense that both metallic and semiconducting nanotubes are produced together as bundles (Krupke et al., 2003). The conductivity of metallic CNT is higher than the semiconductor CNT. Therefore, it is highly desirable to coat NEs with purely metallic CNTs. Owing to their nanoscale geometry, CNTs can interact with and modulate ionic channel behavior, which in turn impacts neuronal characteristics potentially in the long term. For example, single-walled CNTs blocked ion fluxes through potassium ion channels expressed in CHO cells (Park et al., 2003). The authors speculated that the CNTs blocked the channel pore and thus influenced ionic permeability through the membrane. Significant increase in cytoplasmic calcium ions after neurons were depolarized via single-walled CNT (SWCNT) was also reported (Ni et al., 2005). Carboxyl (COOH)-terminated MWCNTs interacted like an antagonist towards three kinds of potassium channels expressed on undifferentiated PC12 cells (Xu et al., 2009). PC12 cells are rat adrenal derived cells that exhibit a distinct neuronal phenotype (Wood et al., 1993), for example voltage-activated inward currents and action potentials (APs). It was speculated that the inhibitory effect on PC12 cells was due to CNTs physically interacting with amino-acid residues of the channel pore. The reduction of calcium and potassium currents by CNTs further demonstrates the impact of carbon nanotube on neuronal physiology (Jakubek et al., 2009; Xu et al., 2009). However, in all of these studies the cell lines were exposed to CNTs that were dispersed in the cell media and available for immediate cellular uptake. As a coating for neural electrode this kind of cellular uptake will not take place if the CNT forms a stable and robust coating during the lifetime of the implant.

5. Neurocompatibility

Biocompatibility, low impedance, and high charge delivery capacity are some of the necessary conditions for successful implantable materials, as we discussed above. These are however not sufficient conditions for neural implants. Neurons could for example grow on substrates and be affected in subtle ways, not immediately perceptible through electrochemical analyses. Here we discuss methods and results that address the more specific problem of "neurocompatibility". This concerns the morphological and electrophysiological characteristics of neurons when exposed to CNT substrates. Most of the results in this area have been obtained in culture and compared against previously established controls. Cell cultures, we argue, are a reasonable experimental model to demonstrate neurocompatibility, as they can be repeated with no loss in generalization.

5.1 Viability and morphology of neurons interacting with CNT substrates

The first results on the interaction of cultured neurons with CNT coated substrates were somewhat controversial: rat hippocampal neurons did not thrive when growing on CNT substrates. This was confirmed by two independent studies: the first (Mattson et al., 2000) admitted some compatibility but also showed long-term (8 days) decreased branching of neuronal processes, while the second (Hu et al., 2004) demonstrated, with quantitative growth cone measurements, that neurite growth in cultured rodent hippocampal cells was different than in control dishes. Similar results were shown for SWCNT substrates and NG108 neuroblastoma (cultured) cells, wherein the cells differentiated but at a reduced rate when compared to tissue-treated polystyrene controls (Liopo et al., 2006).

These early results may have been due to the CNT substrate preparation: highly purified CNTs sheets or yarns were later shown to be conducive to neuronal attachment (Galvan-Garcia et al., 2007). Extension of processes was also comparable to neurons grown on control substrates. Conductivity of the CNT substrate also seemed to matter in terms of neurite outgrowth (Malarkey et al., 2009). Only a small range of conductivities of SWNT-PEG (poly-ethylene-glycol) substrates supported neuronal growth and processes extension. Hippocampal neurons grown on vertically aligned MWCNTs arrays were healthy and growth was comparable to control cultures on plastic Petri dishes (Wang et al., 2006). Successful neuronal growth and interaction with CNTs has now been demonstrated by several groups and their neurocompatibility was confirmed (Ben-Jacob & Hanein 2008; Keefer et al., 2008; Khraiche et al. 2009; Lovat et al. 2005; Lobo et al. 2008).

CNTs present an effective and consistent anchoring site for neuronal attachment and development, and for glial cell differentiation (Jang et al., 2010; Sorkin et al., 2009). CNT coated surfaces are neuro-adhesive in *in vitro* applications (Galvan-Garcia et al., 2007; Lobo et al. 2008). Skillfully designed studies have shown CNT electrodes can be used to position and form stable networks due to mechanically intact contacts between the neurons and the CNTs. The neurons move toward CNT covered surfaces and single neurons position themselves on CNT surfaces. A reasonable hypothesis for the greater affinity of neurons to move specifically towards CNTs coated sites is the higher polylysine adsorption on CNTs. This translates into a more friendly (also more hydrophilic) surface on the CNT than in adjacent areas. The second hypothesis, not necessarily contrary to the first, poses that the nano-mesh structure of the deposited CNTs simulates the structure of the extracellular matrix (ECM). Our current understanding of the electro-mechanical-chemical coupling is very poor. The neuronal affinity to CNTs may be due to the varied nature of CNT production, deposition technique, orientation, and various functionalization ligands.

5.2 Electrical properties of cells impacted by CNT

Neuronal cell cultures grown on SWCNT coated glass substrates showed increased synaptic activity and consequently also increased excitability when compared to control glass substrates. The increase in neuronal activity could be due to a "bidirectional electrotonic current transfer, redistributing the charge along the surface of the membrane" (Lovat et al., 2005). Other studies have also shown that cultured cells on SWCNT substrates maintained their electrohysiological responses comparable to control dishes (Lovat et al., 2005; Mazzenta et al., 2007). However, Cellot et al (2009) demonstrated the presence of an additional somatic membrane depolarization following several action potentials in a burst. An after-depolarization occurs indirectly due to dendritic calcium electrogenesis. This phenomenon is commonly observed during backpropagating action potentials.

"Intimate contacts" were reported between hippocampal neurons and the SWCNTs; this was demonstrated through scanning electron microscope images. These intimate contacts were believed to create a physical channel, which would electrically couple nanotubes to neurons, forming a sort of short-circuit. This short-circuit would ultimately lead to the after-depolarization (Cellot et al., 2009).

Once neurons are plated in primary cell cultures, they extend neuronal processes and make synapses, provided the media is appropriately replenished, and the pH and temperature kept constant (at 7.4 and around 37°C). After 5 to 7 days *in vitro* (DIV) electrophysiological (spontaneous or stimulated) activity can be recorded, and action potentials are the traditional unit of measure in such cultures (Van Pelt et al., 2004). The same electrophysiological signature signal can be measured earlier, around DIV 4, when neurons are exposed to CNT-arrays. Even more interesting, the spontaneous activity increases continously until DIV 7, which is significantly different from the control cultures (Khraiche et al., 2009).

5.3 Stimulation and recording *in vitro* via CNT substrates

Experimental results with CNT-based substrates for stimulating and recording from neuronal cells have been very encouraging. CNT-neuronal interaction has resulted in increased efficiency for signal transmission (Mazzatenta et al., 2007), efficient stimulation (Gheith et al., 2006; Liopo et al., 2006; Lovat et al., 2005), and recordings with high signal-to-noise ratio (SNR) (Keefer et al., 2008 Sauter-Starace et al. 2009)**.** SWCNTs were the first CNTs tested for electrical stimulation of neurons (Liopo et al. 2006). Here dorsal root ganglion neurons were stimulated with SWCNTs deposited on glass coverslips. Another study to test the interaction of cells with carbon nanotubes involved deposition of multilayers of (PAA–/SWCNT+) (PAA: poly(acrylic acid)) on a glass slide. Electrical connections were made with ITO (indium-tin-oxide) strips contacting the SWCNT layer (Gheith et al., 2006) (figure 4). The membrane currents were measured by whole-cell patch clamp. Both of these studies reported fast inward transmembrane currents caused by ionic movement through voltage-gated sodium channels.

CNTs were also used to modify the active surface of MEAs which were then used to stimulate and record from neurons. Vertically aligned CNTs were also used to stimulate embryonic rat hippocampal neurons (Wang et al., 2006). In this case, stimulation current pulses were applied through MWCNT pillars. The evoked APs were optically identified by measuring variance in intracellular calcium using Fluo-4, a calcium indicator. Later, vertically aligned CNTs were embedded in parylene-C to create a flexible MEA (Lin et al., 2009). The flexible CNT-MEAs were able to successfully record spontaneous spikes from the crayfish nerve cord. Ben Jacob et

al (2008) used planar CNTs-MEAs to record from and stimulate neuronal cell lines. APs generated by ganglion cells were recorded by SWCNT- MEAs in greater proportion when compared to geometrically identical Pt-MEAs (Gabriel et al., 2009). CNT probes developed to interface with neurons both intracellularly and extracellularly were comparable in performance to traditionally used glass electrodes with silver/silver chloride wires (Yeh et al., 2009). Steam plasma treatment made MWCNT MEAs hydrophillic (Chen et al., 2010) and were then used to record extracellular APs from a neural cell from crayfish.
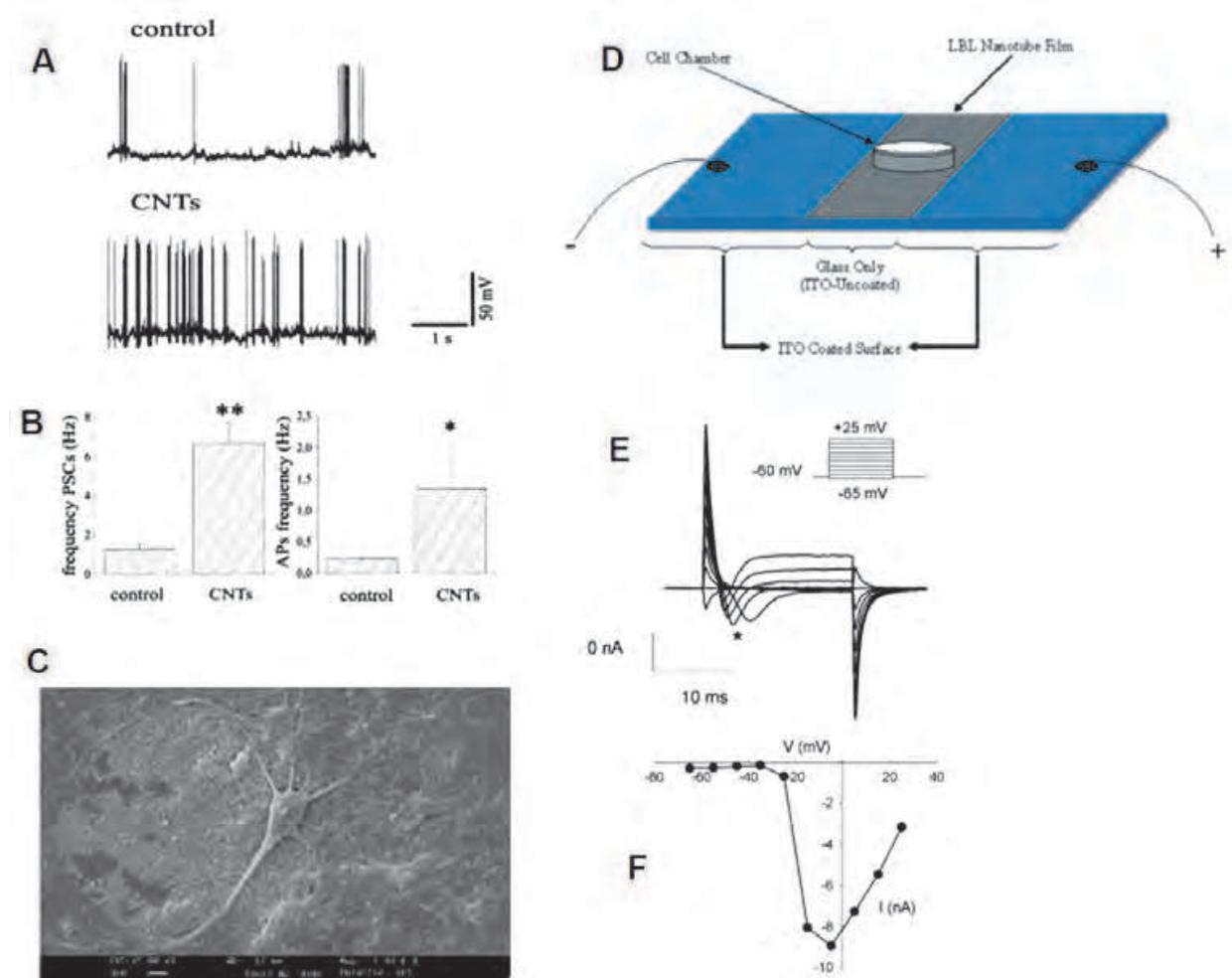
Fig. 4. (A) Spontaneous firing activity recorded in current clamp mode from cultured hippocampal neurons. The activity is enhanced on CNT substrate in comparison to control. (B) Increase in PSCs as well as APs frequency on CNT substrates is shown in a histogram plot. (C) SEM images of neonatal hippocampal neuron after 8 days in culture on coated MWCNT surface on a peptide-free glass. (D) Illustration of the setup used for stimulating a cell in culture via a SWCNT layer. (E) Ionic currents were recorded in the whole-cell voltage-clamp while a (inset) 10 mV increment stimulation protocol was applied through the pipette. (F) Plot of peak inward currents from (E) as a function of stimulation voltage. (A-C) Reprinted with permission from (Lovat et al., 2005), copyright (2005) American Chemical Society. (D-F) Reprinted with permission from (Gheith et al, 2006), copyright (2006) Wiley.

Efforts to demonstrate neurocompatibility of CNT substrates have yielded great results: in summary, cells can be successfully cultured on carbon nanotubes with no damage to their morphology or impairment to their electrophysiological activity. On the contrary: these preliminary efforts have generated questions that point to other modes of interaction between cells and CNTs. We argue that this interface holds many more open questions that can only be addressed through detailed experimental investigations.

6. CNT deposition methods

CNT films coated on neural interfaces have been produced by solvent evaporation, electrochemical deposition, chemical vapor deposition (CVD), layer-by-layer assembly, and electrophoresis. Different groups have used the same techniques with variations in several parameters, either in terms of using a different functionalized group, dispersing solution, co-deposition material material, or substrate. Examples of each method used to fabricate an implantable neural electrode as discussed below For every technique described, the background questions are how straightforward the deposition or growth is, which impacts cost, and how biocompatible the resulting electrode surface and bioavailable species are.

6.1 Chemical vapor deposition

In CVD a hydrocarbon gas provides with carbon atoms that grow on seeded metallic catalysts (Cassell et al., 1999). These catalytic metals are seeded onto metallic tracks realized on a substrate through standard microfabrication techniques; for example, using standard UV photolithography, electron-beam evaporation, and resist lift-off techniques. The substrates are usually silicon, silicon dioxide, quartz and metallic, or any other microfabrication-compatible substrate. The whole setup is then placed in a quartz tube, maintained at atmospheric pressure in a flow furnace. The hydrocarbon gas mixture is passed over the quartz at high temperatures (500°C to 1000°C). The gas catalytically decomposes over the metal particles (iron or nickel) at these temperatures. CNTs are formed on the catalyst layer. The size, geometry, location, quantity, and quality of yield is dependent on the support layer as well as on the metal catalyst (Cassell et al., 1999).

Recently, CVD was used to grow CNTs on penetrating microelectrodes. The tips of commercially available platinum-tungsten wires were electroplated with nickel via potentiostatic electrodeposition. Standard CVD process was used to grow CNTs on the micro electrode surface (Ansaldo et al., 2011) (figure 5(A,B)). An increase in CSC and decrease in impedance was reported for CVD-CNT electrodes. A similar CVD technique was used to grow CNTs vertically on MEAs (Wang et al., 2006) (figure 5(G,H,I)).

6.2 Electrochemical

Electrochemical deposition can be used to co-deposit CNTs with metals, conductive, and non-conductive polymers. The deposition of a conductive coating onto an electrode is achieved by putting a charged species on the electrode to be coated. The electrode is immersed into a solution containing oppositely charged desired species to be deposited. The electric current drives the counter ions to the electrode, oxidizing and reducing the desired species on the electrode surface. Co-deposition CNTs serves two purposes: enhancing the conductivity by lowering impedance and larger interacting surface area by increasing porosity. This in turn boosts the CSC and decreases the impedance. Electrochemical deposition can be used to coat variety of substrates and geometrical shapes.
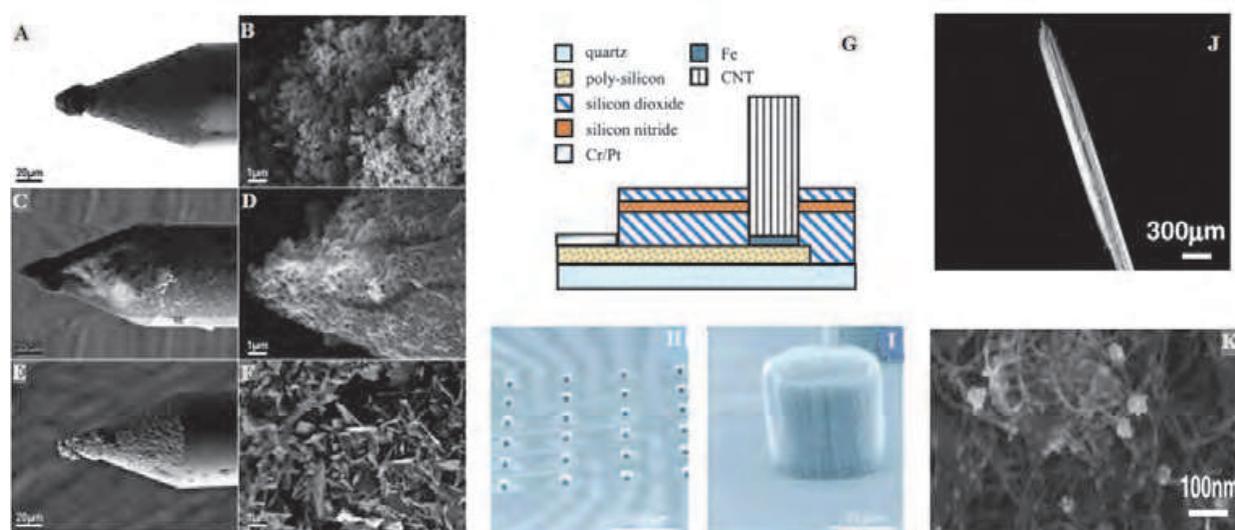
Fig. 5. SEM images reveals the morphology of (A,B) CNT-CVD, (C,D) Poly-pyrrole-CNT, (E,F) Gold-CNT coated penetrating microelectrodes. (G) Schematic of microelectrode array (MEA); (H) array of microelectrodes; (I) one microelectrode with forest-like CNTs extending vertically outside the plane of the MEA. (J) SEM image of stainless steel electrode after MWCNT deposition. (K) SEM image at higher magnification. Homogeneous random entangled arrangement of MWCNT over the metal substrate is observed, which increases the effective area of the electrode. (A-F) Reprinted with permission from (Ansaldo et al., 2011), copyright (2011) American Chemical Society. (G-I) Reprinted with permission from (Wang et al., 2005), copyright (2005) American Chemical Society. (J,K) Reprinted with permission from (Minnikanti et al., 2009), copyright (2009) Institute of Physics.

Keefer et al (2008) coated MEAs and penetrating wire electrodes with three different electrochemical CNT deposition methods using voltage controlled methods. The three coatings differed in functionalization and preparation methods. For all coatings, experimental results showed an increase in the charge storage capacity and a decrease in impedance when compared to bare wire electrodes. The morphology of the obtained surfaces, depending on the coating, is dramatically different. Figure 5 (A-F) shows examples of nanorough surfaces and of nanoporous surfaces (Ansaldo et al., 2011).

6.3 Electrophoresis
Electrophoresis is used in our laboratory to deposit CNTs onto metallic substrates (stainless steel and gold). Electrophoretic deposition (EPD) occurs due to the movement of charged particles in a suspension under the influence of an applied electric field. In the case of CNT EPD, the applied field deforms the particle double layer distortion and causes particle coagulation on the substrate. The coagulation is derived from the Derjaguin-Landau-Verwey-Overbeek (DLWVO) theory and is governed by London-Van der Waals forces (Sarkar & Nicholson, 1996). For each set of EPD experiments, a DC voltage of approximately 2V is applied between a bare stainless steel electrode (anode) and a bare gold electrode (cathode). The distance between the two electrodes needs to be kept at 1 mm or less in order for the deposition to take place during the first five to ten minutes. The field used in our experiments yields a stable cohesion of MWCNTs (figure

5(J,K)) onto metallic substrates (Boccaccini et al., 2006), (Minnikanti et al., 2009). The modulus of impedance of the bare stainless steel electrode decreases by two orders of magnitude for most of the frequencies tested. The cathodic charge storage capacity (CSCc) of bare electrodes significantly increases after MWCNT deposition, for example in one case the CSCc increased from 2.18 $\mu C/mm^2$ to 7.15 $\mu C/mm^2$ after deposition. Electrodes can be aged (for months) by exposing them to air, but they still maintain high CSCc. Some CNT-coated electrodes show oxygen uptake and further enhance their charge delivery capacity during the aging process.

EPD is a versatile procedure. While the results may be extremely sensitive to deposition parameters, factorial design of experiments can be applied in order to find an optimum deposition protocol, depending on substrate and CNT solution desired. In particular for NEs, water based dispersions are preferred. They can be used in EPD, thus reducing the presence of harsh toxic chemicals in the final implantable electrode. Further steps are commonly taken to improve adhesion, as for example microwave heating (Su et al., 2010).

6.4 Layer-by-layer assembly

Layer–by-layer assembly is the alternate adsorption of charged poly-ions on a substrate to create a thin coating. Each adsorption step leads to the formation of a monolayer poly-ion species. Poly-ions are formed after a poly-electrolyte dissociates in an aqueous solution. Jan et al (2009) used MWCNTs in poly(sodium styrene sulfonate) (PSS) and Poly vinyl alcohol (PVA) as alternate adsorption layers. The substrate used was a 400 μm diameter ball electrode made of platinum-iridium (Pt-Ir). The deposition process consisted of alternately immersing in each solution, followed by a rinse with deionized water and dried using an air jet. PVA/MWCNT coated electrodes decreased the impedance and increased the CSC of the Pt-Ir. Also, a higher CSC was reported for the PVA/MWCNT electrodes in comparison to polyethylenedioxythiophene and iridium oxide having identical thickness (Jan et al., 2009). Others have also reported using this method to deposit CNT on glass coverslips to grow and stimulate neuronal cultures (Gheith et al., 2006). This method can be used on arbitrarily shaped objects. This technique offers simplicity and flexibility. A variety of structures can be coated with thickness controlled at a nanoscale level.

6.5 Solvents and sprays

These two techniques have been used to deposit CNTs on planar substrates. A traditional substrate here is a glass coverslip. Using external electrical connections to these substrates neuronal cultures can be stimulated. These techniques have not been used to coat implantable NEs, as adhesion and long term stability haven't been characterized yet.

6.5.1 Solvent

This method involves dispersing CNTs in organic solvents. CNTs are deposited onto substrates as thin films as the organic solvent evaporates. Lovat et al (2005) suspended functionalised MWCNTs in DMF and then deposited the solution as drops via a pipette on top of the glass coverslips. MWCNTs attached to the glass surface as the solvent evaporated. The advantage of this method is that it is economical and operates at room temperature and pressure.

6.5.2 Spray

Compressed air can break down an aqueous media into a fine layer of deposited mist on a heated substrate. The heat causes the aqueous portion of the deposited mist to evaporate and thus leaves a thin continuous film. The deposition thickness is dependent on the flow rate of the solution and speed at which the nozzle moves towards the substrate. Malarkey et al (2009) deposited CNTs on glass coverslips by spraying an aqueous media of SWCNT-PEG using an airbrush. The SWCNT-coverslips were heated to 160° C to form uniform films (Malarkey et al., 2009). The advantages include economical, flexible procedure and the usage of aqueous based solutions.

7. CNT coated implants: *in vivo* studies

The ultimate test of an implantable electrode is the experimental demonstration of charge transfer after surgery. Hopefully many months later, that same electrode will still transfer charge to and from the central nervous system, without significant inflammation or mechanical disruption to the tissue: this will be the *litmus* test for that material. Throughout this chapter we have taken the reader across a wide field: we have touched on electrochemistry, principles of charge transfer, biocompatibility, mechanical and electrical requirements for electrodes, and methods for deposition of CNTs onto conductive and non-conductive substrates. We have attempted to present an unbiased description of the available literature in the field of neural interfaces mediated by CNTs, and have pulled insights from adjacent fields which, we believe, impact the engineering of such electrodes.

We turn now to the *litmus* test mentioned above: a deft insertion, seamless integration with the central nervous system, and then the electronic and ionic flow across the electrode-tissue interface is the objective of these CNT-coated electrodes. The first time a CNT electrode was used in an animal, chronically implanted, as a recording electrode was in 2008. Keefer et al (2008) reported the successful recording of local field potentials (LFPs) via MWCNT electrodes in two different animal models. LFPs are defined as the combined extracellular activity from multiple neurons. Two types of electrochemically deposited MWCNT electrodes were implanted in the motor cortex of anesthetized rats: MWCNT-Au-tungsten wire stereotrode, and MWCNT/Ppy-modified stainless steel electrodes. Both MWCNT and control electrodes recorded neural activity from a common source. However, single neuron spikes measured via MWCNT electrodes had larger amplitude and those electrodes (MWCNT) presented greater sensitivity for detecting neuronal activity.

MWCNT coatings using covalent chemistry were also investigated by that same research group (Keefer et al., 2008). The acyl-chloride modified nanotubes were covalently attached to amine-coated stainless steel electrodes. These electrodes along with control (uncoated electrodes) were implanted in the V4 region visual cortex of a monkey. The measured LFP traces (figure 6(A,B)) for both electrodes show a strong temporal correlation, aindicative of a common origin of the measured signal. Here also the measured spike amplitude of the MWCNT-coated electrode was larger than in controls. Power spectra analysis shows that the MWCNT electrode data had more power in the frequency range of 1-300 Hz. Inspection of the surface morphology of explanted MWCNT electrodes revealed mechanical stability even after penetrating through the dura matter.
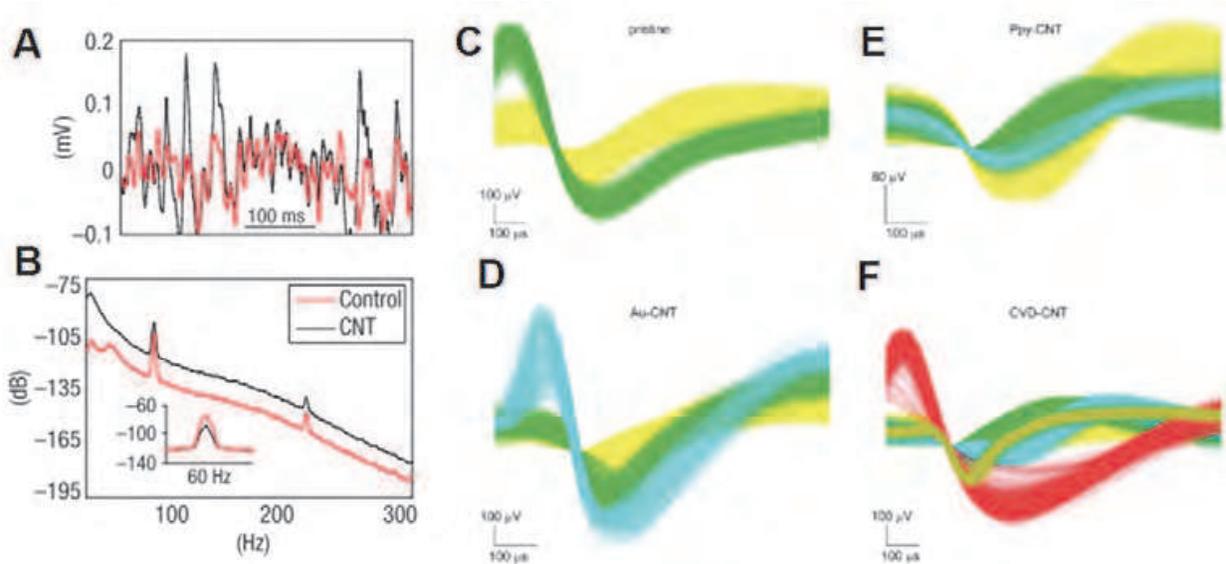
Fig. 6. (A) LFP traces. (B) Power spectral density (PSD) analysis from CNT coated compared with control electrodes. PSD with 60-Hz line noise subtracted. The LFP amplitude and average power is greater with lower 50 Hz for CNT electrodes in comparison to controls. Inset: PSD with 60-Hz line noise subtracted .(C-F) Single unit activity from an acute session, using non-coated (pristine) and coated (Ppy,Au,CVD)-CNT electrodes. Sorted units are color coded, each representing one neuron. (A-B) Reprinted with permission from (Keefer et al, 2008), copyright (2008) Nature, (C-F) Reprinted with permission from (Ansaldo et al, 2011), copyright (2011) American Chemical Society.

Ansaldo et al (2011) recorded intracortical neuronal activity in rat cortex with three types of CNT coated electrodes and compared it to a control electrode. Quartz-insulated platinum/tungsten wires with CVD grown CNT coatings (CVD-CNT), PPy-CNT and Au-CNT nano composites were used as electrodes. This group is the first to record single unit neural signal *in vivo* via CVD deposited CNTs on microelectrodes in animal models (figure 6(C-F)). The impedance of the CNT electrodes did not change significantly before of after the recordings. The authors conclude that the CVD deposited CNT is the best electrode in terms of robustness, but the use of high quantities of nickel will prevent the chronic use of these electrodes.

Our group developed electrophoretically deposited MWCNT electrodes, with the explicit requirement of wide frequency stimulation of deep brain structures (Minnikanti et al., 2010). We conducted acute implants in the rodent hippocampus to evaluate the *in vivo* performance of the MWCNT electrodes, and to compare that performance with the *in vitro* results. *In vivo* and *In vitro* (phosphate buffered saline, pH 7.4) analysis follows the same regime, with *in vitro* tests done both prior and subsequently to implanting the electrode. The analysis consisted of 30 CV cycles (50 mV/s, -0.7 V to 0.7 V) followed by an EIS cycle (5 mHz to 50 kHz, 10 mVpp). The developed MWCNT electrodes maintained their CSCc and impedance *in vivo* (figure 7). EIS performed *in vitro* and *in vivo* showed that the impedance modulus was not significantly affected when electrodes are implanted in deep brain structures (figure 7). This behavior is unlike that observed in traditional electrodes, where the charge decreases, and the impedance increases, during and after implantation.

We also investigated the immediate response to low-frequency stimulation by evaluating the transcriptional levels of IL-1β and TLR2 using reverse-transcriptase polymerase chain

reaction (RT-PCR). Two key molecules involved in the signaling cascades for inflammatory responses to damage in the CNS are the receptor TLR2 (Owens et al., 2005) and the pro-inflammatory cytokine IL-1β (Rothwell et al., 2000). IL-1β was upregulated as part of the inflammatory response to low-frequency stimulation, but TLR2 did not significantly increase in stimulated tissue when compared to controls. The inflammatory molecules initially active at the electrode–nervous tissue interface did not increase the impedance of MWCNT electrodes. Our investigation of the surface morphology post-implantantion shows that the MWCNT mesh withstands implantation. This is indicative of the robustness of the adhesion of nanotube film to the stainless steel surface and of the successful implant and extraction procedures used during the implant.

Tissue reaction determines the viability of a material as an implant material. A recent study, the first of its kind, investigated the chronic (12 weeks) response of muscle to implanted aligned carbon nanotubes (ACNTs) (Nayagam et al., 2011). Although not implanted in CNS, this study is highly relevant as it tests immoblized MWCNT arrays and not freely floating MWCNTs. Male guinea pigs were implanted with ACNT/SIBS (poly[styrene-b-isobutylene-b-styrene]) arrays. Two controls were used: SIBS sheets coated with stannous octoate as an internal positive control and poly-tetra-fluoro-ethylene as a negative controls. Histopathology was performed in order to assess the host response to controls as well as to the CNT material. The immobile CNTs did not elicit a significantly different host response when compared to controls. However, dislodged CNTs elicited an immune response and were phagocytosed. Also the immobile ACNTs had low levels of surface fouling. These results are encouraging towards the usage of CNTs as implantable electrodes and emphasizes on the necessity of a stable CNT deposition.

A chronic study involved implanting electrochemically co-deposited PPy/SWCNT on platinum wire electrodes in rat brains for 6 weeks (Lu et al., 2010). Bare platinum wires were used as controls. Tissue response was conducted by characterizing the expression of GFAP and NeuN immunostaining around the implant site. GFAP is a specific marker of astrocytes and NeuN reflects neuronal densities. Higher GFAP expression is indicative of elevated inflammatory processes. GFAP expression was lower for the coated electrode in comparison to the bare electrode. The neuronal density was higher as well as the neurons surrounding the implant were larger in comparison to bare electrode, signifying better neuronal survival. However, it has been shown that low impedance and high charge PPy-CNT coatings degrade when subjected to extensive periods of standard clinical stimulation pulses (Ansaldo et al., 2011). Thus the improved performance of co-depositing CNTs may be lost due to the instability of PPy.

Flexible CNTs MEAs were implanted in the motor region of a non-human primate (Sauter-Starace et al., 2009) for a chronic study. The MEAs consisted of polyimide support with alternate titanium nitride (TiN) and CNT electrodes. CNTs were deposited by CVD process. ECoG signals were recorded over the period of one year. The power spectra of recorded activity shows that CNT electrodes sensed greater amount of signal than the TiN electrodes. Absence of acute reactive gliosis covering the MEAs was reported.

A CNT-NE was recently used as interface with the nervous system of an insect (Tsang et al., 2010). The authors microfabricated flexible neuroprosthetic probes (FNPs) with CNT-Au nanocomposites. The FNPs were a part of a telemetry system interfacing with the insect's CNS. The implant was successfully tested in adult as well as in pupal stage moths. The applied stimulation via CNT-FNPs was able to force an unbound flying insect to turn.

In vitro experiments recreate a limited environment faced by a NE. Thus acute and chronic *in vivo* studies are crucial for evaluating the true performance of a NE. Although few *in vivo* studies have been conducted for CNT based recording and stimulating NEs, so far they show promising results. Collectively, these studies encourage the use of CNTs for the development of neuroprosthetic devices as long as they are immobilized. More chronic studies need to be performed before the judgment is passed on the performance and effect of CNT-based implantable NEs.
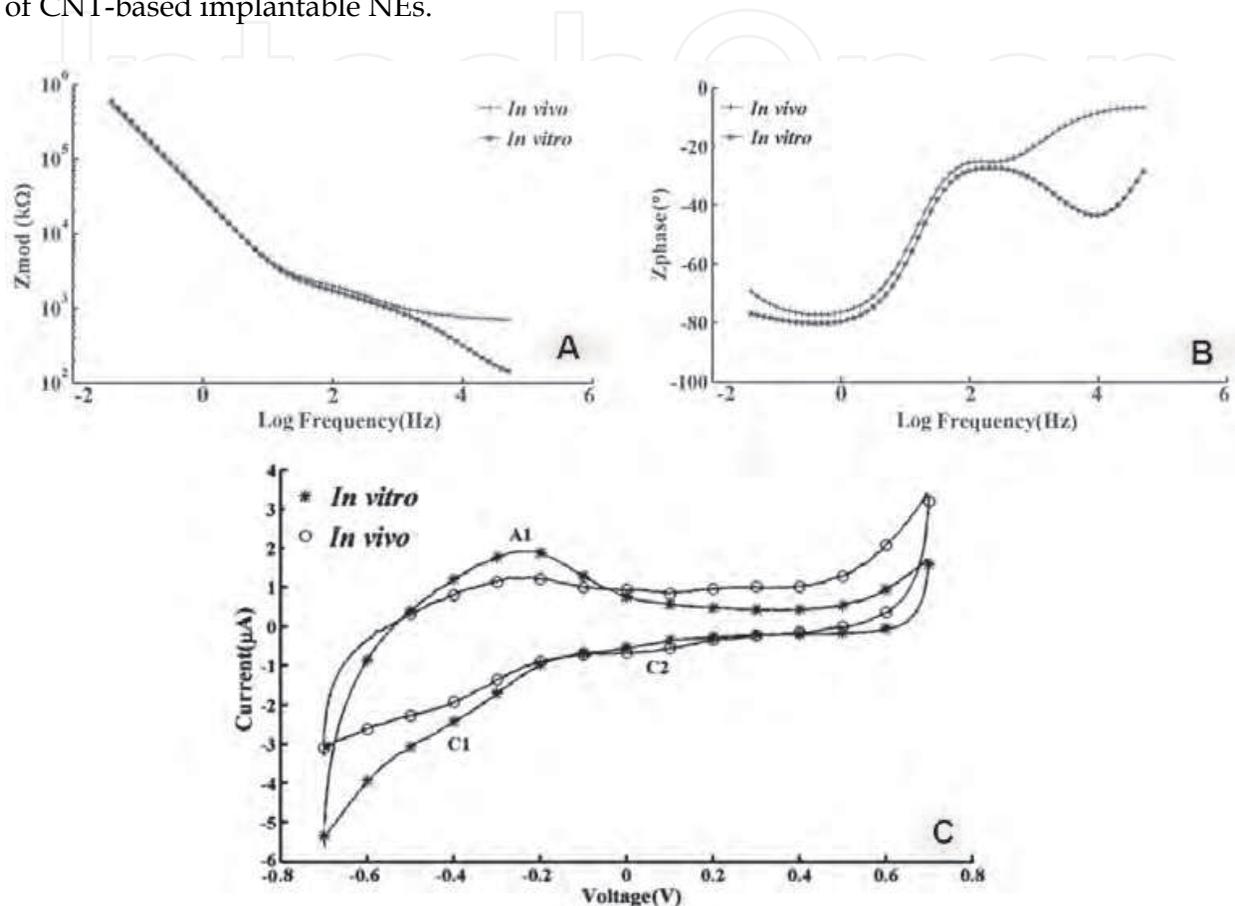
Fig. 7. Bode plots comparing (A) impedance modulus and (B) impedance phase (C) CV of a single bare stainless steel electrode (◦) to a MWCNT electrode (+). Measurements use a three electrode setup in PBS (pH 7.4) solution with Ag/AgCl as the reference electrode and platinum foil as a counter electrode. Lowering of impedance is observed over the measured frequency range. For the bare stainless steel electrode, $CSCc = 0.488$ mC cm^{-2}; for the MWCNT-coated electrode, $CSCc = 0.996$ mC cm^{-2}. Reprinted with permission from (Minnikanti et al., 2010). Copyright (2010) Institue of Physics.

8. Conclusions

Current NE substrates used clinically are metallic (Greenberg & Rezai, 2003). In the past few years, issues with the processibility of conductive polymeric materials were overcome, and they became viable alternatives to metal electrodes (Cui & Zhou, 2007; Cui et al., 2001; Richardson-Burns et al., 2007). However, stability of conductive polymers is questionable (Ansaldo et al., 2011; Peixoto et al., 2009). CNTs, with their distinctive properties, can improve the performance of NE, as a coating over the metallic electrodes (Minnikanti et al., 2010) or when electrochemically co-deposited with conductive polymers (Keefer et al., 2008).

Over a decade ago the first CNT-neuronal experiment was performed (Mattson et al., 2000). Still, the true nature of the CNT-neuron interface remains an open question. Certain unique interface features offer an edge over current NE materials. Interaction with CNTs rearranges the charge along the membrane surface to increases neuronal excitability (Lovat et al., 2005). This could be particularly useful for NEs. If passive contact increased the excitability of neurons *in vivo* this would reduce the required charge to stimulate neurons. The enhanced cell adhesive property of CNTs may present an improved tissue–electrode interaction. This may reduce the need for the adhesion promoting layer, for example laminin or polylysine. Recently simulation results of stimulating the brain using a CNT based optically activated stimulator was presented (Mohy-Ud-Din et al., 2010). The idea was to use the implantable CNT stimulator that transduces light into electrical current. Unlike the traditional opto-genetic approach, in this case the genetic modification of neurons is not necessary.

Electrodes based on MWCNTs and deposited through electrophoresis were developed in our lab and presented a very interesting observation not related to the CSC, but to the preservation of the underlying substrate electrochemistry (Minnikanti et al., 2009). We have tested the same deposition method with different substrates, and all of them kept their characteristic reduction-oxidation peaks upon MWCNT deposition. Those CNT electrodes present an interesting *in vivo* behavior: they maintained their CSC *in vivo* and *in vitro* in acute scenarios (Minnikanti et al., 2010). The inflammatory response from the tissue hinders the charge transfer in acute and chronic situations. Tracking of inflammatory response *in vivo* is of importance if the objective of the implant is charge transfer. We have demonstrated that certain inflammatory molecules, initially active at the electrode-nervous tissue interface, do not prevent charge transfer neither increase the impedance of MWCNT electrodes in acute implants (Minnikanti et al., 2010). This effect of molecular interaction occurring at the interface of MWCNTs and neural tissue needs to be further investigated. This will help identify the key molecules in this unique behavior and thus create a model for testing the potential of any material as a neural implant or electrode.

Characterization of the CNT-neuron interface, at least electrically, has been focused on using SWCNTs as substrates (Gheith et al., 2006; Liopo et al., 2006; Mazzatenta et al., 2007). Many other aspects need to be investigated such as interacting protein conformational changes, variation in depolarization or hyperpolarization, and protein expression and adhesion when in contact with CNTs. Care needs to be taken before correlating or extrapolating the data. CNTs show promise as a next generation neuroprostheitc material. These are diamonds in raw waiting to be polished the *right* way.

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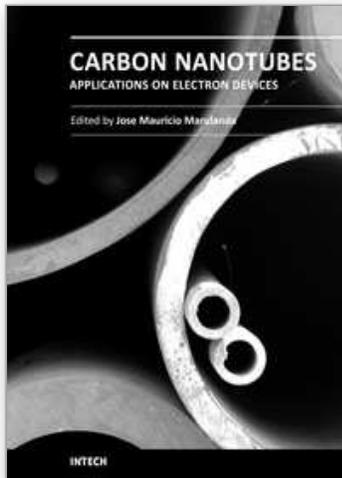
Carbon Nanotubes Applications on Electron Devices

Edited by Prof. Jose Mauricio Marulanda

Carbon nanotubes (CNTs), discovered in 1991, have been a subject of intensive research for a wide range of applications. In the past decades, although carbon nanotubes have undergone massive research, considering the success of silicon, it has, nonetheless, been difficult to appreciate the potential influence of carbon nanotubes in current technology. The main objective of this book is therefore to give a wide variety of possible applications of carbon nanotubes in many industries related to electron device technology. This should allow the user to better appreciate the potential of these innovating nanometer sized materials. Readers of this book should have a good background on electron devices and semiconductor device physics as this book presents excellent results on possible device applications of carbon nanotubes. This book begins with an analysis on fabrication techniques, followed by a study on current models, and it presents a significant amount of work on different devices and applications available to current technology.

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