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## Electrochemical Biosensing with Carbon Nanotubes

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### 1. Introduction

The nanobioelectrochemistry is a new interdisciplinary field which aims to combine the purposes of bionanotechnology with electrochemistry methodology. It focuses on the study of the electron transfer (ET) kinetics that occur at biointerfaces during redox reactions Chen et al. (2007). The ET results in a electron current that can be easily quantified allowing accurate and high sensitive measurements. These properties are extremely relevant on biological field in which the lacking of quantitative measurement is often a bottle neck in developing new processes.

The majority of biosensors is based on one or more bioactive molecules used in conjunction with an electrode. A redox reaction could be detected electrochemically by three different measurements: i) direct redox of a molecule involved in biological environments; ii) redox of a small mediator species that shuttles between the bioactive molecule and the electrode; iii) direct ET between the biomolecule redox site and the electrode (Fig. 1). Bioactive molecules are referred as such enzymes that require cofactors (as FAD or NADH) for catalytic activity. These bioactive molecules ensure high specificity due to structure recognition between enzymatic protein and substrate and high sensitivity due to high redox catalytic efficiency of cofactors. This latter mechanism of bioelectrochemical sensor is less common because it requires an intimate coupling between electrodes and biomolecules preserving their biological activity. On the other hand, direct electron transfer mechanism has intrinsic advantages with respect to the other two mechanisms because the electrochemical signal can be quantitatively related to a biological phenomenon without signal dissipation generated by the additional mediator. It is well known that the mediator can either react on the electrode or diffuse away in the bulk solution leading to a general sensitivity lowering. In this context, achieving direct ET could not be straightforward and for this reason, modification of biomolecules or electrode surfaces through the use of novel nanostructured materials as mediator and the engineering of biointerfaces has been reported Hartmann (2005); Hernandez-Santos et al. (2002); Kohli et al. (2004); Wang (2005). The integration at nanoscale length is of paramount importance for reducing the probability of mediator charge dissipation at the interface towards the bulk. The new interface realized comprehending the system nanostructure/biomolecule can be defined as the nanostructured biointerface.

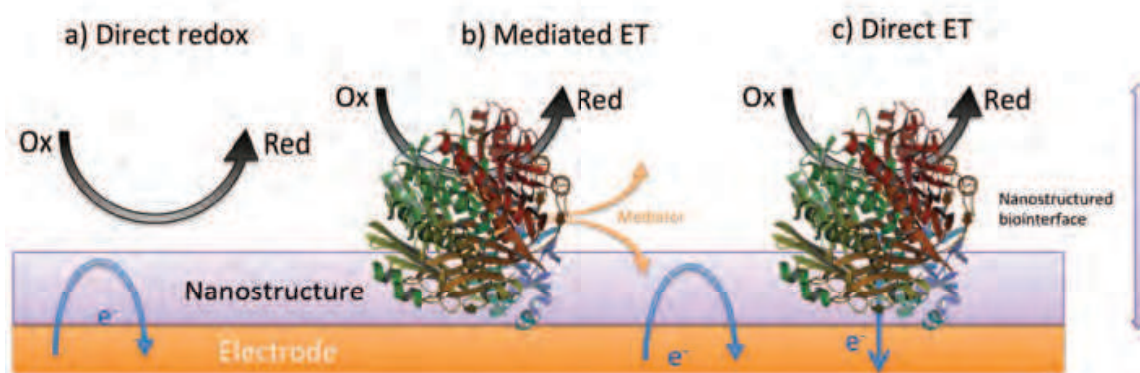


Fig. 1. Scheme of electron transfer (ET) processes on nanostructured electrode surfaces. The system biomolecule + nanostructure forms the nanostructure biointerface. a) Direct redox reaction involving bioactive molecules present in solution; b) mediated ET between electrode surface and nanostructured biointerface; c) direct ET between electrode surface and nanostructured biointerface.

Among nanomaterials, carbon nanotubes could be a perfect solution to overcome the efficiency limitation described above and for this reason are widely used for fabricating the functional biointerfaces enhancing the sensors response. CNTs are well-ordered, nanomaterials with a high aspect ratio; typical lengths are from several hundred nanometers for single-walled carbon nanotubes (SWCNTs) and several to hundreds of nanometers for coaxial multi-walled carbon nanotubes (MWCNTs) Dresselhaus et al. (1996); Smart et al. (2006). Their use is justified by recent studies that demonstrated that CNTs can enhance the electrochemical reactivity of CNT electrochemical systems Musameh et al. (2002); Zhao et al. (2002) and the ET rates of biomolecules Gooding et al. (2003); Yu et al. (2003), accumulate commonly used biomolecules Wang, Kawde & Musameh (2003), and alleviate surface fouling effects for molecules absorption in presence of complex media Musameh et al. (2002). To take advantage of these remarkable properties, CNTs need to be chemically functionalised following oxidation protocols in order to obtain ordered nanostructure interface. Vertical alignment of oxidized nanotubes on electrodes shown to be one of the most exciting and promising strategy of modification of electrodes with CNTs.

Among various attractive characteristics, it was mainly the electric properties of carbon nanotubes that stimulated large scale industrial production of CNT-based materials. However, the electronic response of individual nanotubes is reported to be sensitive to various parameters, such as the synthesis method, defects, chirality, diameter and degree of crystallinity Dresselhaus et al. (2005). It is known that solids with high aspect ratios can produce three-dimensional networks when incorporated into polymer materials. When added as well-dispersed fillers, they provide a conductive path through the composite. Therefore, carbon nanotubes were shown to increase both thermal and electric conductivities of polymers at low percolation thresholds (up to a few weight percents).

On the other hand, carbon nanotubes can be linked to metal or semiconductive surfaces in order to enhance sensitivity, specificity and usage as sensors as we will report further.

Carbon nanotubes may interact with biological environments such as proteins, DNA or neurochemicals. Electronic properties strongly affect the efficiency of interaction of nanotubes with biosystems because of nanotubes defects, metal impurities from fabrication and percentage of doping in bulk materials may alter metabolites detection while biosensing.

Recent studies demonstrated that CNTs enhance electrochemical reactivity Musameh et al. (2002); Zhao et al. (2002) but a chemical functionalization is needed in order to take advantage of these fundamental properties. As will be discussed further, covalent and non covalent functionalization methods are reported to modify interactions between electrodes and CNTs. Finally, it is note worthy to consider the induced field effect in developing carbon nanotubes based biosensors: when polarizing carbon nanotubes modified electrodes in saline media, current flows very close to the electrodic surface thus perturbing linked biosystem Alivisatos (2003). This would lead to modification of theoretical electronic nanotubes properties for application in which a single nanotube or a small quantity of CNTs is needed (Field-Effect transistors Dastagir et al. (2007); Martinez et al. (2009), nanoprobos Burns & Youcef-Toumi (2007); Wong et al. (1998), patch clamp Mazzatenta et al. (2007)).

The aim of this chapter is to review the most relevant contributions in the development of electrochemical biosensors based on carbon nanotubes (CNTs) particularly focusing on the modification of properties and possible applications arising from when a vertically alignment of CNTs is chosen. Therefore, after a brief introduction on the origin of the peculiar electronic properties of nanotubes, an in-depth study on preparation, characterization and biosensing application on vertically aligned SWCNTs modified electrodes is shown. Finally a section focused on future perspectives is provided in which we will analyze the possibility to modify existent materials with CNTs forward a bulk modification strategy. Also a section on the possibility to integrate the CNTs electrochemical devices in microfluidic platforms is presented. This latter technology allows to diminish the average dimensions of the substrates reducing cost and time of analysis and to enhance the selectivity while performing experimental investigations in high-throughput fashion.

## 2. Electrochemical biosensing with carbon nanotubes

The nanostructure of the nanobiointerface has several fundamental requirements: i) the thickness has to be comparable with respect to average biomolecule systems; ii) it could posses an intrinsic high conductivity to diminish any added resistance; iii) it could be chemically functionalised to assemble the nanostructured with the bioactive molecule realizing the nanobiointerface. Carbon nanotubes (CNTs) respond to all of these required features because of their tunable dimensions, their good electric properties and their easy chemistry.

Recently carbon nanotubes (CNTs) have also been incorporated into electrochemical sensors Britto et al. (1999); Campbell et al. (1999); Che et al. (1998); Luo et al. (2001); Wang et al. (2001). CNTs offer unique advantages including enhanced electronic properties, a large edge plane / basal plane ratio and a rapid electrode kinetics. In general, CNT-based sensors have higher sensitivities, lower limits of detection and faster electron transfer kinetics then traditional carbon electrodes. Many variables need to be tested and then optimized in order to create a CNT-based sensor. The performance can depend on the synthesis method of the nanotube, CNT surface modification, the method of electrode attachment and the addition of electron mediators.

Electrochemistry implies the transfer of charge from one electrode to another one. This means that at least two electrodes constitute an electrochemical cell to form a closed electrical circuit. However, a general aspect of electrochemical sensors is that the charge transport within the transducer part of the whole circuit is always electronic. By the way, the charge transport in the sample can be electron-based, ionic, or mixed. Due to the curvature of carbon

graphene sheet in nanotubes, the electron clouds change from a uniform distribution around the C-C backbone in graphite to an asymmetric distribution inside and outside the cylindrical sheet of the nanotube. When the electron clouds are distorted, a rich  $\pi$ -electron conjugation forms outside the tube, therefore making the CNT electrochemically active Meyyappan (2005). Electron donating and withdrawing molecules such as  $\text{NO}_2$ ,  $\text{NH}_3$ , and  $\text{O}_2$  will either transfer electrons to or withdraw electrons from single-walled carbon nanotubes (SWCNTs). Thereby giving SWCNTs more charge carriers or holes, which increase or decrease the SWCNT conductance Meyyappan (2005).

Recent studies demonstrated that CNTs can enhance the electrochemical reactivity of important biomolecules Andreescu et al. (2008); Erokhin et al. (2008); Musameh et al. (2002); Zhao et al. (2002), and can promote the electron-transfer reactions of proteins (including those where the redox center is embedded deep within the glycoprotein shell) Gooding et al. (2003); Yu et al. (2003). In addition to enhanced electrochemical reactivity, CNT-modified electrodes have been shown to be useful to accumulate important biomolecules (e.g., nucleic acids) Wang, Kawde & Musameh (2003) and to alleviate surface fouling effects (such as those involved in the NADH oxidation process) Musameh et al. (2002). The remarkable sensitivity of CNT conductivity to the surface adsorbates permits the use of CNTs as highly sensitive nanoscale sensors. These properties make CNTs extremely attractive for a wide range of electrochemical biosensors ranging from amperometric enzyme electrodes to DNA hybridization biosensors. To take advantages of the remarkable properties of these unique nanomaterials in such electrochemical sensing applications, the CNTs need to be properly functionalized and immobilized. There are different ways for confining CNT onto electrochemical transducers. Most commonly, this is accomplished using CNT coated electrodes Liu et al. (2008); Luong et al. (2004); Vairavapandian et al. (2008); Wang, Kawde & Musameh (2003); Wang, Musameh & Lin (2003) or using CNT / binder composite electrodes Rubianes & Rivas (2003); Sljukic et al. (2006); Wang & Musameh (2003). The CNTs driven electrocatalytic effects and the increasing use of modified CNTs for electroanalytical applications have been recently reviewed Vairavapandian et al. (2008).

Among the traditionally used electrode materials such as graphite, gold or mercury, CNTs showed better behavior than the others which also have good conducting ability and high chemical stability. CNT-based electrochemical transducers offer substantial improvements in the performance of amperometric enzyme electrodes, immunosensors and nucleic-acid sensing devices. The greatly enhanced electrochemical reactivity of hydrogen peroxide and NADH near the proximity or on the CNT-modified electrodes makes these nanomaterials extremely attractive for numerous oxidase- and dehydrogenase-based amperometric biosensors. For example, vertically aligned CNTs structures can act as molecular wires to allow efficient electron transfer between the underlying electrode and the redox centers of enzymes. The CNT transducer can greatly influence for enhancing the response of the biocatalytic reaction product and provide amplification platforms carrying multiple enzyme tags: it is shown that the vertical orientation is required for obtaining high ET results in such experiments.

For this reason the next section will provide a schematic view for the realization of vertically aligned SWCNTs modified electrodes particularly focusing on critical features and open issues.



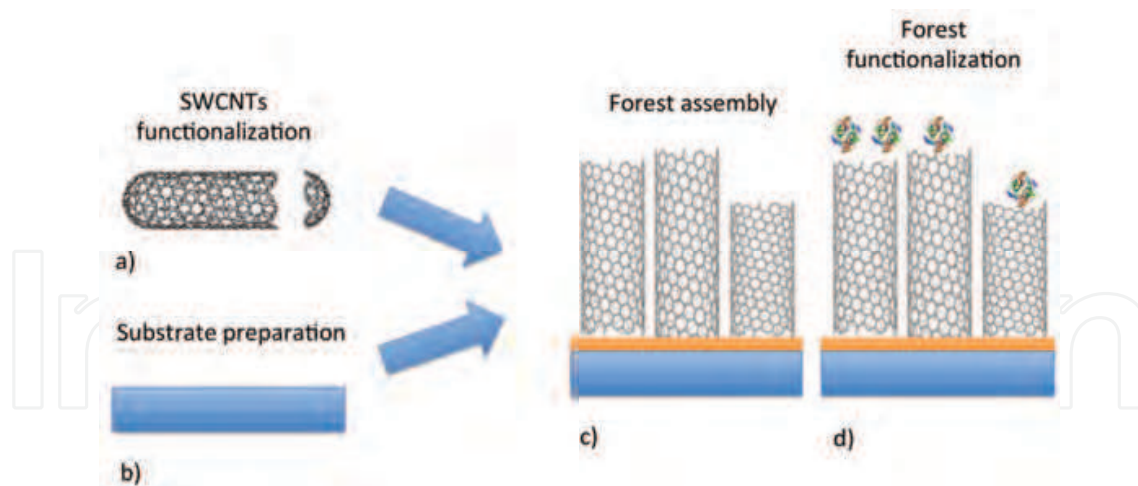


Fig. 2. Steps involving the fabrication of SWCNTs forests based sensors via chemical assembly. a) Substrate preparation; b) SWCNTs functionalization; c) Forest assembling; d) Forest functionalization.

### 3. Fabrication of vertically aligned SWCNTs modified electrodes

Among carbon nanotubes modified electrodes, surface modification strategy is one of the most used because of the high versatility in chemical modification of substrates and further functionalization, facile impact, low cost and low wastes. In particular, the most promising approach is to develop self-assembled monolayer of CNTs perpendicular oriented to the surface of the electrode in order to realize a forest of carbon nanotubes Diao & Liu (2010). There are a lot of works in which it is demonstrated that the vertical alignment is a good choice for assembling because it can enhance the performance of many nanotube-based devices such as emitters in panel displays Bonard et al. (1998); De Heer et al. (1995), nanoprobe as tips protrusion for optimum high resolution images collection Wong et al. (1998) and in the electrochemical biosensing field because of the good conductivity of the nanotubes, their small diameter and high aspect ratio Chou et al. (2005); Diao & Liu (2005); Diao et al. (2002); Gooding et al. (2003); Yu et al. (2006). It has also been found that a vertical orientation enhance the electron transfer reaction rates at the electrodes with respect to a random dispersion of nanotubes on the surface Chou et al. (2005). Finally forests can be simply functionalised with enzymes and specific redox reaction involving biomolecules can be achieved Liu et al. (2005); Patolsky et al. (2004).

In this chapter we will focus only on chemical self-assembly technique for forests production because, with respect to other conventional approaches (such as CVD, arc-discharge and laser ablation) it shows highly flexibility in topographical control of nanotubes vertical assembly in term of CNTs superficial density and micro and nanopatterns. In addition, conventional approaches may produce forests with endless nanotubes, randomly curled and highly tangled also requiring expensive experimental setups.

The general scheme for obtaining a biosensor based on forests of SWCNTs (the most used in this field of research) via chemical assembly, is presented in Fig. 2. Many steps are involved in the fabrication of a forest of SWCNTs:

1. Substrate preparation
2. SWCNTs functionalization

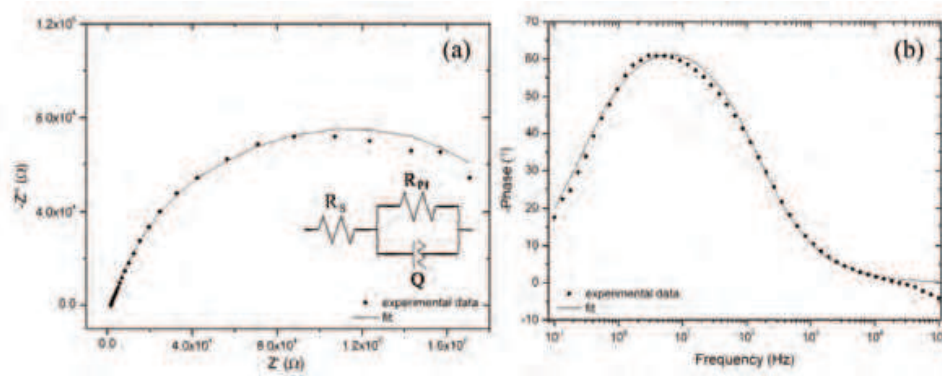


Fig. 3. Typical EIS spectra for a gold electrode after electrochemical pretreatment protocol. In panel (a) it is shown the Nyquist plot representing the semicircle typical of a clean polarized electrode in solution whereas the inset represents the model used for fitting experimental values ( $R_s$  is the uncompensated resistance solution,  $R_{p1}$  and  $Q$  the associated polarization resistance and real capacitance respectively of the gold electrode); panel (b) shows the Bode phase plot: a resonance peak for the circuit at ca. 10 Hz is found.

3. Forest assembling
4. Forest functionalization

### 3.1 Substrate preparation

Different substrates are chosen for preparing SWCNTs forests: different metals (gold De Heer et al. (1995); Lamberti et al. (2010); Nan et al. (2002); Patolsky et al. (2004); Sheeney-Haj-Ichia et al. (2005) and silver Wu et al. (2001)) or other materials (silicon Yu et al. (2007; 2006), glass Chattopadhyay et al. (2001); Jung et al. (2005), Nafion film Wei et al. (2006)). Substrates cleanness is of paramount importance for achieving an optimum assembling of nanotubes: organic molecules or oxides adsorbed on the surface would affect the efficiency of nanotube coupling. Normally metal substrates (gold in particular) undergo a rigid cleanness protocol that foresees first a mechanical polishing with alumina or similar, then a chemical treatment in strong mixtures like piranha solution and/or an electrochemical treatment step Carvalho et al. (2005). It is note worthy that it is the electrochemical cleanness the most important step in the protocol: for example we have found that electrochemical impedance spectra (EIS) of clean gold surfaces after electrochemical step reveal that polycrystalline gold surfaces are the cleanest and smoothest with a lesser amount of oxides (Fig. 3). Also it is known that impurities affect polycrystallinity, adhesion of metals on substrates and reproducibility: for example, physical enhanced chemical vapor deposition (PECVD) deposition allows to obtain clean films because depositions are performed in UHV Lamberti et al. (2011).

### 3.2 SWCNTs functionalization

Carbon nanotubes prior to being covalently linked to the surface, need to be purified and functionalised because metal nanoparticles and carbonaceous impurities byproducts are still present from production step. Also it is well known that  $sp_2$  carbon atoms of sidewall of nanotubes are more stable than the  $sp_2$  ending atoms: for this reason, it was demonstrated by Liu et al. Liu et al. (1998) that any chemical attack of the tubes would start from the ends of the tubes and proceeds shortening the nanotubes from the defects produced shortening the tubes.

There are many purification strategies in literature such as mixed acids bath Chou et al. (2005); Diao et al. (2002), piranha solution Liu et al. (1998); Ziegler et al. (2005), ozonation Rauwald et al. (2009), phosphomolybdic acid Warakulwit et al. (2008), persulfate solution Liu et al. (2007), pyrolysis Gu et al. (2002) and electron beam irradiation Rauwald et al. (2009). Carbon nanotubes are not only cut and purified when treated in these oxidant conditions but carboxylic functions would create at damage sites: in particular it has been shown by our group that a distribution of oxygenated species would be present on the surface of nanotubes, from carboxylic functions to aldehydes Lamberti et al. (2010). We also showed that nanotubes can be shortened in a controlled way by monitoring the temperature of oxidation bath instead of the time as people normally do: in such circumstances we can monitor not only the length of the nanotubes (obtained by AFM with a standard deviation of some tens of nm maximum) but also the distribution of oxygenated species that appear at the sidewalls by XPS and Raman measurements (Fig. 4). Carboxylated nanotubes may be easily functionalized thanks to chemical versatility of -COOH group. As we will discuss after, acid groups are of paramount importance for coupling nanotubes to the electrode surfaces and to link proteins and other biomolecules in fabricating biosensors.

As final conclusion we can assume that the oxidative cutting by prolonged sonication in strong oxidation has several advantages such as ease of operation, simple equipment and no special requirements. Moreover, this oxidative method allows to obtain short nanotubes in fast times.

### 3.3 Forest assembling

Surface condensation method (Fig. 5 a) and b)) is the most used fabrication technique for assembling SWCNTs forests in literature because the coupling efficiency is resulted the best Diao & Liu (2010). It develops in forming firstly the self-assembled monolayer (SAM) of small bridge molecules on the substrate (alkanethiols or mercaptoalcohols) and then a reaction involving carbodiimide (CDI) reactions took place at the acid functions. SWCNTs are dissolved in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) and reaction take place at 60 °C. Usually three different CDIs are used depending on the type of solvent used for dissolving nanotubes: DCC (N,N'-Dicyclohexylcarbodiimide), EDAC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide) and DIPC (N,N'-Diisopropylcarbodiimide) (Fig. 5 d)). As we can see in Fig. 5 c), CDI reaction provides to the formation of an amidic/esteric bond between the C atom of the nanotube and the N (or O) atom of the SAM on the electrode. The active intermediate reagent is the O-acyl isourea that is transformed into amide when a nucleophilic substitution happens in presence of an amine or an alcohol. That is the problem because the O-acyl isourea can undergo to a intramolecular rearrangement: this byproduct, N-acyl urea, is totally stable in most common solvents (typical 5%-10% wt is dissolved). For this reason people try to minimize this unwanted reaction by stabilizing O-acyl isourea adding to reaction solution some pyridine.

Also, the urea molecules deriving from CDIs are not always soluble in common solvents: the corresponding urea for DCC, Dicyclohexylurea (DCU) is totally insoluble in most of organic solvents and filtration is necessary to remove it; the corresponding urea for EDAC, the EDAU, is soluble in water and for this reason it is used for peptide synthesis, whereas DIPU, the corresponding urea for DIPC, is quite soluble in organic solvents and the remains are normally removed by rinsing with solvent.

It is note worthy that, for this reason, forests fabricated with DCC reagent (almost all) can



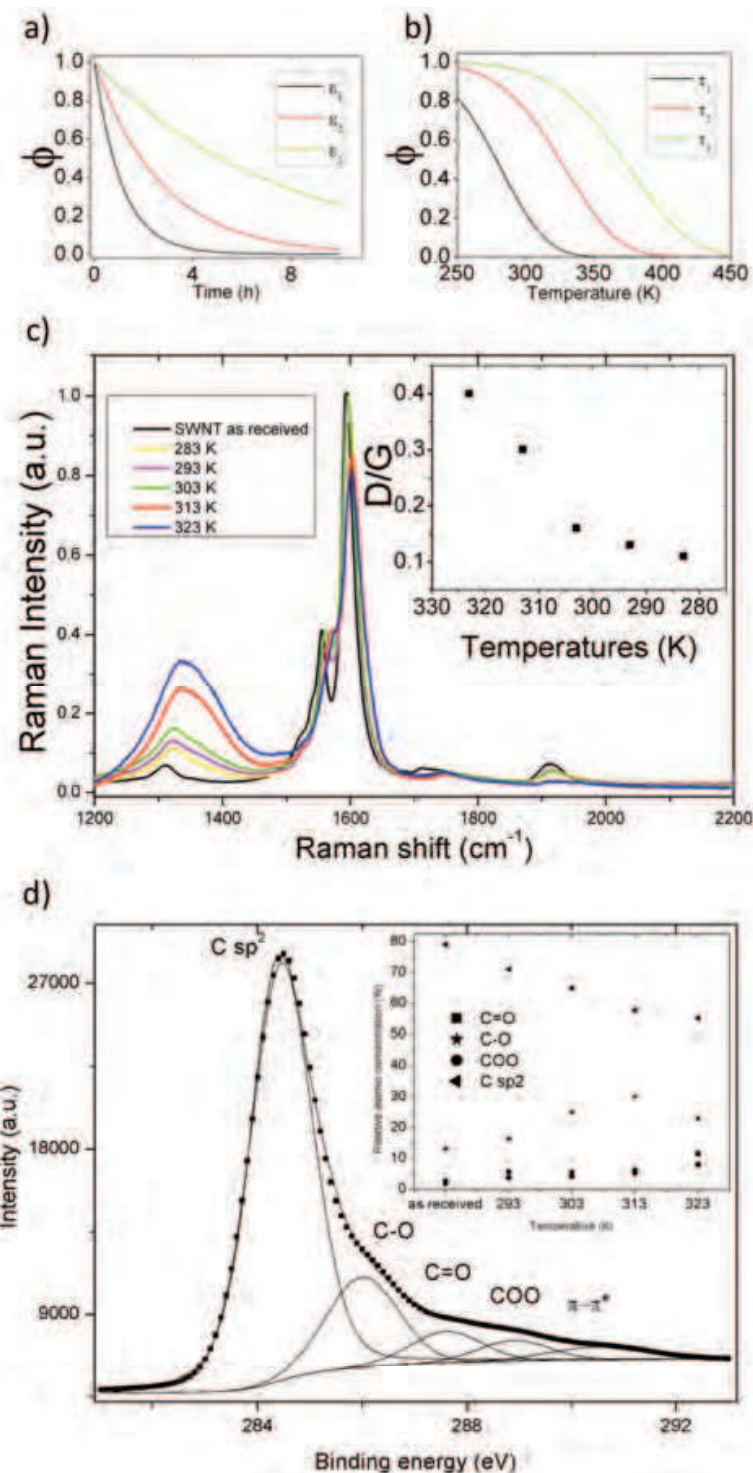


Fig. 4. a) Time-dependence of the fraction of oxidized carbon ( $\phi$ ); b) temperature-dependence of  $\phi$ ; c) Raman spectra (exciting line 633 nm) of SWCNTs oxidized at five different temperatures. Inset reports the ratio of the D/G peak intensities as a function of temperature and the dotted line indicates the D/G ratio for the pristine nanotubes; d) X-ray photoemission spectrum of carboxylated carbon nanotubes. The spectrum reveals that there are many partially oxygenated species in addition to the -COO species. The inset graph shows the temperature dependence of the C sp<sup>2</sup> component and the corresponding enhancing of the oxygenated species.

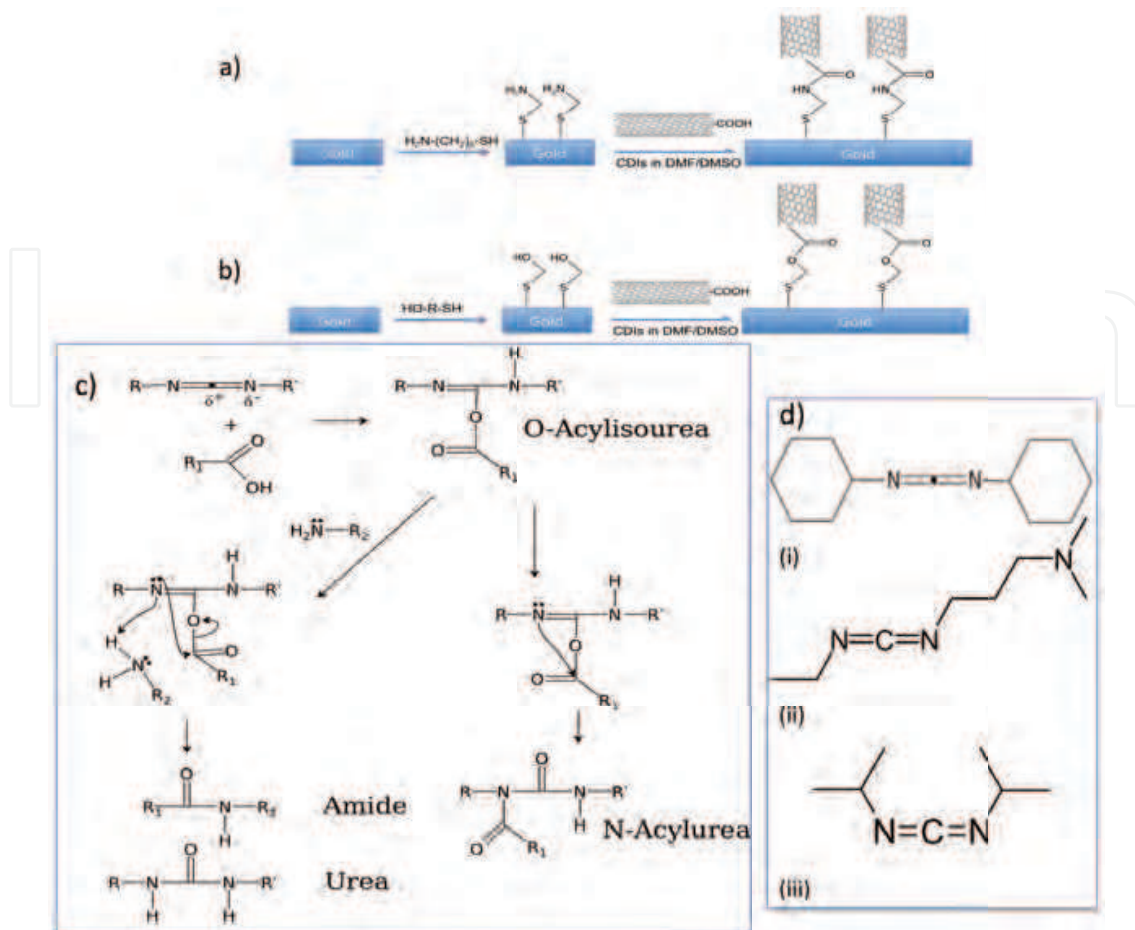


Fig. 5. a) Surface condensation method described within the text using alkanethiols or b) mercaptoalcohols. c) Chemical scheme of reactions occurring when forming amidic/esteric group in fabricating SWCNTs forests: N-Acylisourea is the unwanted by-product of the reaction that is almost insoluble in all common solvents; d) structural formula of the existing carbodiimides: (i) DCC (N,N'-Dicyclohexylcarbodiimide), (ii) EDAC (N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide) and (iii) DIPC (N,N'-Diisopropylcarbodiimide).

not be clean: so in our work Lamberti et al. (2010), we used DIPC instead of common DCC in order to avoid unwanted reagents on samples. In Fig. 6, AFM 3D images of SWCNTs forests at different height are presented. Vertical aligned SWCNTs have been prepared through amide or ester formation using DCC or EDAC on gold substrates Chou et al. (2005); Diao & Liu (2005); Diao et al. (2002); Gooding et al. (2007; 2003); Huang et al. (2006); Nan et al. (2002); Nkosi & Ozoemena (2008); Ozoemena et al. (2007); Patolsky et al. (2004), silicon Huang et al. (2007) and glass substrates Bonard et al. (1998); Jung et al. (2007; 2005). For substrates different from gold the only modification in the technique is the modification of the substrate: typically silicon surface are treated with alkylaminotrimethoxysilane Huang et al. (2007), a compound that contains an amino group. Before amination, substrate need to be modified with hydroxyl groups in order to realize a organosilane SAM on the surface Ulman (1996). Other methodologies were used for fabricating SWCNTs forests. First of all, the "Au-S bonding" production scheme that implies that the thiols were previously covalently attached to the acidic ending groups of the nanotube and afterwards CNTs were put in contact

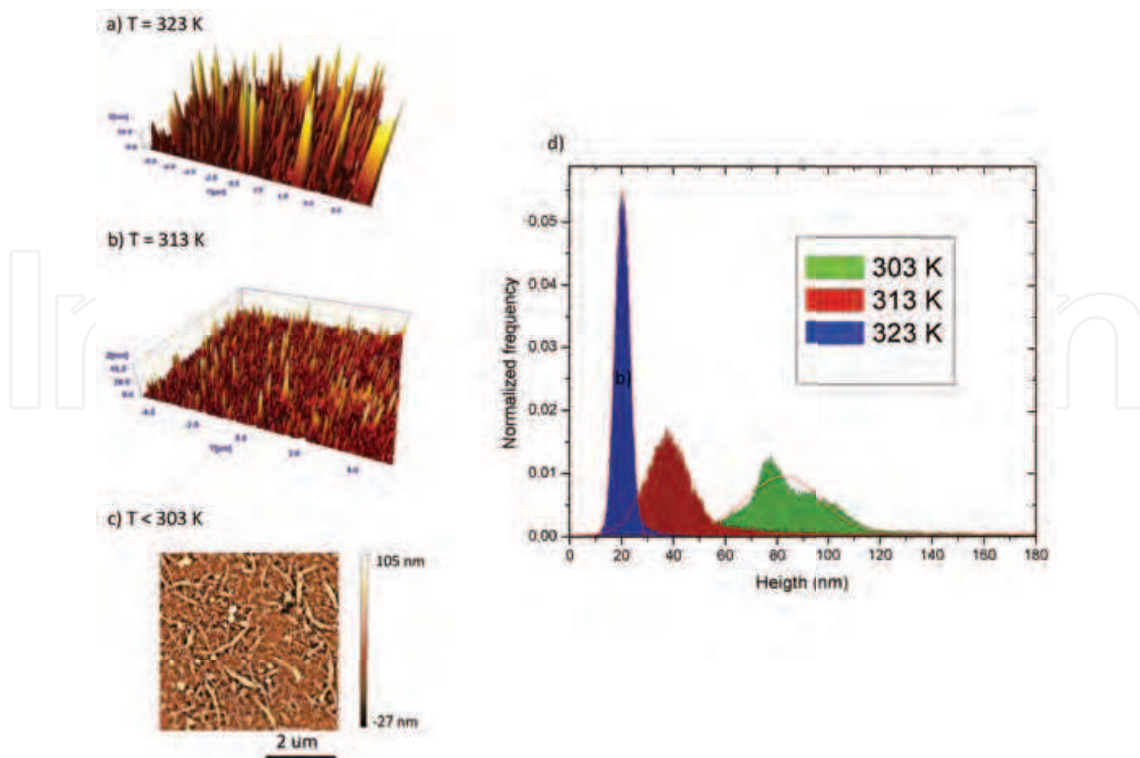


Fig. 6. Atomic force microscopy 3D image of SWNTs forests built at different temperature conditions: a) at 313; b) at 323; c) the AFM 2D image of randomly dispersed carboxylated SWNTs treated at 283 K oxidation process; d) normalized frequency of height of SWNTs measured with AFM for three different temperatures. At 283 and 293 K there is no evidence of SWNT forests.

with gold substrates allowing the formation of Au-S bond Liu et al. (2000). Van der Waals interactions between sidewalls of nanotubes are recognized as the main forces that can prevent the nanotubes to horizontal deposition. The coupling efficiency was relatively low and in order to improve the surface coverage of nanotubes people switch to surface condensation strategy and the electrostatic interaction strategy.

This latter takes advantage of the electrostatic forces between carboxylated SWCNTs and surface. This is possible because carboxylated nanotubes after oxidation are negatively charged ( $-\text{COO}^-$ ) allowing electrostatic attraction between them and positively charged surfaces. Papadimitrakopoulos et al. Wei et al. (2008; 2006); Yu et al. (2005; 2006) develop several works in which using a metal-assisted self-assembly technique modifying electrodes with  $\text{Fe}^{3+}$ . This strategy was used to fabricate carbon nanotubes forests on different substrates such as silicon Chattopadhyay et al. (2001), Nafion-modified silicon Wei et al. (2006), glass Chattopadhyay et al. (2001), gold Wei et al. (2007) and graphite Yu et al. (2003).

#### 4. Forest characterization

Once forests have been fabricated on different substrates, there is the problem to characterize these nanometric structures. Here we summarize the most relevant contribution to the characterization techniques used in literature: Atomic Force Microscopy (AFM) imaging, Raman spectroscopy and X-ray Photoelectron Spectroscopy (XPS). Also Fourier transform infrared spectroscopy (FTIR) Diao et al. (2002) and Quartz Crystal Microbalance (QCM)

Chattopadhyay et al. (2001) are used but they are not widely used as the above methods. Table 1 shows the principal characterization techniques used in literature and the results that can be obtained.

Technique	Result
AFM	Morphology and surface coverage
Raman	Composition and SWCNTs orientation
XPS	Composition and SWCNTs degree of difectuality
FTIR	Information of surface functionalities
QCM	Information on mass change during the assembling

Table 1. List of the main techniques used for characterizing SWCNTs forests. Effective results of each technique is also presented.

#### 4.1 AFM imaging

AFM is considered one of the most wanted technique for the characterization of forests because of AFM provides direct imaging of the nanostructures fabricated on electrodes. AFM imaging analysis can provide the topography of the forest, understanding if nanotubes are deposited in bundles or individually by the deconvolution of the AFM tip by simple geometry considerations Diao et al. (2002); Gooding et al. (2003); Liu et al. (2000); Yu et al. (2003). AFM data also provide informations about the surface coverage, the surface distribution and height of the forests evaluating the coupling efficiency Chattopadhyay et al. (2001); Diao & Liu (2005); Diao et al. (2002); Gooding et al. (2003); Lamberti et al. (2010; 2011); Liu et al. (2005; 2000); Patolsky et al. (2004); Yu et al. (2007). Despite the fact AFM can reach a subnanometric resolution, roughness of the substrates, not ideally surfaces and thermal noise would limit AFM to identify forests whom average height is not higher than a few nanometers.

#### 4.2 Raman spectroscopy

Carbon nanotubes are Raman active Ajayan (1999): SWCNTs are identified by radial breathing modes at Raman shift ca.  $200\text{ cm}^{-1}$ . Also Raman spectroscopy is very sensible: only one nanotube, in principle, can be detectable. For this reason, Raman scattering can be used for monitoring or confirming the presence of nanotubes on samples but it does not give any information about the surface coverage or surface distribution of nanotubes. Nevertheless, Papadimitrakopoulos et al. Chattopadhyay et al. (2001) shown that using polarized Raman spectroscopy it would be possible to obtain informations about the orientation of the nanotubes on samples: the intensity was the highest when the polarization of the incident laser is perpendicular to the substrate and the lowest when parallel giving evidence to the vertical alignment of the deposited nanotubes.

Raman scattering also can give informations about quantity of defects as we have previously reported Lamberti et al. (2010): D-band (Raman shift  $1330\text{ cm}^{-1}$ ) intensity enhances its value increasing oxidation temperature of nanotubes i.e. the number of defects enhances when nanotubes are treated in higher oxidative temperature conditions.

#### 4.3 XPS

X-ray Photoelectron Spectroscopy is mostly used for studying surfaces. It provides informations about the chemical bonds involving the atoms that are present on the surface of a material. For this reason, carbon atom would have a different XPS peak if linked to an N



atom or an O atom. Also, different hybridization of the same atom give different XP spectra. So, by coupling this technique to Raman spectroscopy we can obtain different informations about oxygenated species at the sidewalls when nanotubes are in an oxidized form. Lamberti et al. (2010) shown that increasing nanotube oxidation temperature the relative percentage of C sp<sup>2</sup> component diminishes and also, -COO contribution enhances whereas a distribution of oxygenated species is always present (phenols, pyrans, ethers, anhydrides). XPS can also provide informations about the quantity of bonds in comparison to C-C sp<sup>2</sup>. Therefore, it can also quantitatively describe the defect density in CNTs but if Raman measurements are available, informations about defects density in the CNTs surface can be better detected because of Raman spectroscopy is recognized as one the most suitable technique for characterizing carbon based materials. As a final conclusion, Raman and XP spectroscopies provide informations about the quantity and quality of defects in oxidized nanotubes respectively.

## 5. Electrochemical characterization

The knowledge of electrochemical properties of carbon nanotubes modified electrode is of paramount importance for obtaining informations about the applicability of such electrodes in sensing, biosensing, nanoelectronic devices, field emitters and nanoprobe. The goal is to study the charge transfer (i.e. the electrons' flow) between the electrode and redox species and the electrochemical response of vertical alignment in function of its features such as height and surface density. Redox species can be free-moving in solution or covalently bonded to the SWCNTs.

### 5.1 Redox species dissolved in solution

Before discussing the works reported in literature for this kind of study, it is note worthy to understand what steps are included in the electron path from the redox species to the underlying collecting electrode. We can assume three different steps as defined in Fig. 7: (i) the electron transfer between redox center and forest, (ii) the electron flow across the nanotube, (iii) the electron jump between nanotube and electrode. In this context, Diao et al. (2005) proposed a charge transfer model based on tunneling process.

It is noted that the heterogeneous electron transfer (HET) at the open ends of SWCNTs should be remarkably more rapid than that at the sidewalls Cui, Lee, Raphael, Wiler, Hetke, Anderson & Martin (2001); Li et al. (2002). It was shown that the bridge molecule SAM blocks the electron transfer between the redox probe in solution and the underlying electrode. Also it has been demonstrated that the vertical alignment could promote the ET though there is an insulating monolayer in between them Diao et al. (2002) as described in the typical behavior in Fig. 8 (panel 1.A). This phenomenon is also confirmed in EI spectra: in Fig. 8 (panel 1.B) it is shown a Nyquist plot representing the impedance behavior of electrodes modified with an insulating molecule and a SWCNTs forest. The insulation increases the associated polarization resistance of the circuit whereas the forest assembling decreases it.

From this preliminary consideration scientists try to study the effect in heterogeneous electron transfer (HET) kinetics in samples in which the surface coverage and height vary. Gooding et al. (2005); Chou et al. (2005); Liu et al. (2005) investigated the ET kinetics of Fe(CN)<sub>6</sub><sup>3-/4-</sup> at SWCNTs forests: he found that ET occurs much easier in vertically aligned carbon nanotubes with respect to randomly dispersed SWCNTs. Also, he correlates XPS results in determining

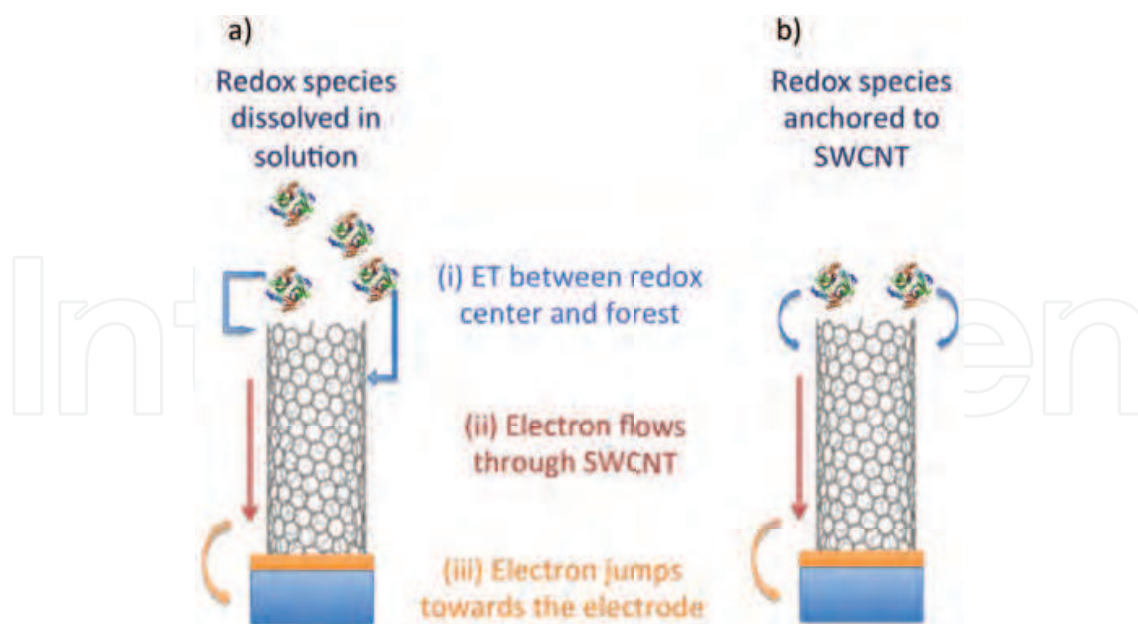


Fig. 7. Schematic representation of ET phenomena occurring in two different situations involving SWCNTs forests: with the redox center free-diffusing in solution and directly linked to the open ends of the nanotube.

that the oxygenated species at the open ends are responsible for high ET. Gooding has also shown Gooding et al. (2003) that aligned nanotubes acts as molecular wires and added no significant electrical resistance to the electron transfer process. Willner's group Patolsky et al. (2004); Sheeney-Haj-Ichia et al. (2005) assumed that defect on the sidewalls may introduce local damage in p-conjugation lowering the ET rate but because of the short height of the forests, the electrical resistance is very short and for this reason negligible. Lamberti et al. in a very recent work Lamberti et al. (2011) gave a good contribution in this sense: our work allows to show that SWCNTs forests fabricated with nanotubes of different heights have significantly different ET kinetic, i.e. shorter is the forest, higher is the ET and of course, smaller is the resistance. Fitting electrochemical impedance spectra with Randles modified cell model, let us to know ET dynamics of system. This result is motivated because forests produced with our temperature-controlled method, allow to obtain nanotubes with a narrower height distribution and more sensible data can be collected.

The electron transfer dynamics between SWCNTs and substrate is the most important step. Diao and colleges Diao & Liu (2005) shown that the adsorbed SWCNTs act as many "electron relay stations" that mediate electrons between the metal electrode and redox centers. Also it is noted that the linking bonds at the ends of the tubes ensure an high electron transfer between nanotubes and surfaces Chidsey et al. (1990); Cui, Primak, Zarate, Tomfohr, Sankey, Moore, Moore, Gust, Harris & Lindsay (2001); Cui et al. (2002); Finklea & Hanshew (1992); Koehne et al. (2004) but Gooding et al. Chou et al. (2009) reported that the electron-transfer rate at the nanotube-modified electrodes decayed exponentially with distance when the chain of the molecule bridge is increased. In this context our recent study on the combined effect on height and surface density of nanotubes give an overall point of view of HET dynamics in SWCNT forests Lamberti et al. (2011). This work starts from the result of Willner's group Patolsky et al. (2004) that found that mixing cysteamine (CYS) layer with 2-mercaptoethanol (ME) molecule to modify gold substrate, would enhance following nanotubes coupling efficiency.

It is shown that ester reaction in these experimental conditions is slower than the amide formation. Taking advantage of this result, we tried to control the surface density by choosing different ratios concentration of CYS/ME determining that a slow amount of ME is necessary to obtain highest values of ET kinetics. AFM images shown that samples with a low relative concentration of CYS would present SWCNTs forests with a broader height distribution: angle contact measurements reveal that nanotubes coupling efficiency is strongly linked to interface processes. The final aim of this study was to actually conclude the study on HET dynamics in SWCNTs forests, determining the optimum conditions for fabricating forests as used in particular for biosensing.

### 5.2 Redox species anchored to forests

Carbon nanotubes can be used for directly reaching redox centre in species in which ET is very low: in such circumstances, high-sensitivity electrochemical and bioelectrochemical sensing can be performed.

Redox enzymes Gooding et al. (2003); Liu et al. (2005); Patolsky et al. (2004), electroactive complexes Nkosi & Ozoemena (2008); Ozoemena et al. (2007); Yu et al. (2008) and ferrocene Flavel et al. (2009; 2008); Gooding et al. (2007); Yu et al. (2007) were rightly attached to vertical aligned SWCNTs. Ferrocene, a molecular redox probe usually used for ET studies because of its ideal Nerstian behavior, was attached by Shapter and coworkers Yu et al. (2007) and they found that the presence of nanotubes in samples modified with ferrocene with or without the forest, improve the ET. This result is very important because it suggests that vertical alignment of carbon nanotubes can transport electrons. Moreover, other works show that orientation of nanotubes affect ET properties: for randomly dispersed carbon nanotubes the ET is low with respect to vertical alignment due to difficulty of hopping for electrons from one nanotube to another Gooding et al. (2007).

The possibility of anchoring enzymes or biomolecules would open the way to making biosensing with carbon nanotubes forests: Gooding works and Willner's are the milestones in this sense Gooding et al. (2003); Patolsky et al. (2004). Gooding et al. Gooding et al. (2003) were the first who tried to attach an enzyme to the open ends of a nanotube: they studied the ET kinetics in vertical aligned SWCNTs on which were immobilized microperoxidase (MP-11) and even if ET efficiency is dependent on the spacer thickness, this is negligible when this is in the submicrometric range as in the case of carbon nanotube spacers. Nevertheless, Willner and colleges Patolsky et al. (2004) anchored a reconstructed Glucose Oxidase (apo-GOx) to the opened ends of nanotubes and they found that nanotubes with an average shorter length would increase ET in oxidizing glucose dissolved in solution (Fig. 8). This is in contrast to the previous thesis of Gooding work in which he found that no contributes are to be recognized to length of nanotubes and further work has to be done for solving the dispute.

Willner's work also shown the possibility of using nanotubes as ET mediators for oxidizing or reducing species in solution, as demonstrated by Ozoemena et al. Ozoemena et al. (2007) who oxidize dopamine taking advantage of linking an iron complex to the open ends.

As final conclusion, we can assume that vertical alignment is the best choice for obtaining high direct ET of species in solution or anchored to the forests with respect to other strategies of nanotubes modification. Also they can act as charge transfer mediators for performing redox reactions of species in solution.

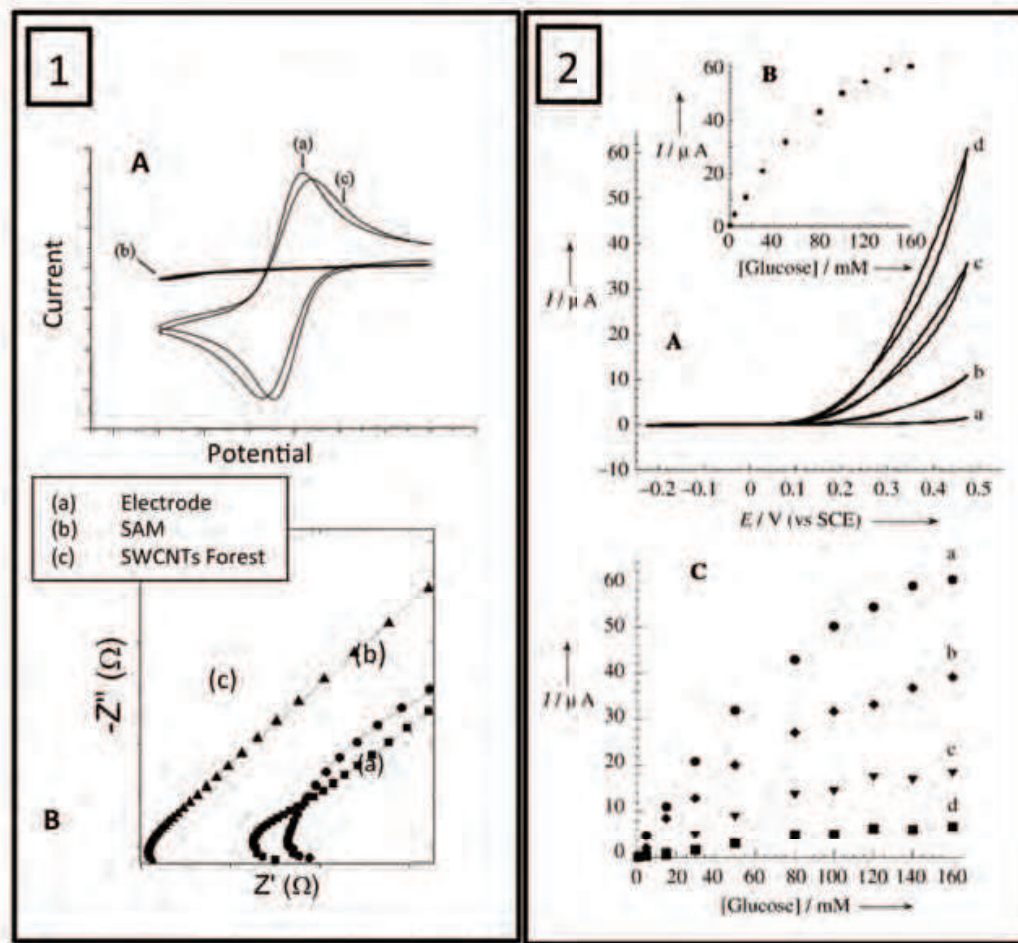


Fig. 8. Schematic view of the electrochemical measurements performed with SWCNTs forests in presence of a redox species. A. Redox species dissolved in solution: typical i) CV and ii) EIS showing the oxidation and the reduction of a redox probe on (a) an electrode, (b) a modified electrode with SAM and (c) a SWCNTs forest modified electrode. B. Redox species anchored to SWCNTs. A) Cyclic voltammograms corresponding to the electrocatalyzed oxidation of different concentrations of glucose by the GOx reconstituted on the 25 nm long FAD-functionalized CNTs assembly: a) 0 mM glucose, b) 20 mM glucose, c) 60 mM glucose, d) 160 mM glucose. Data recorded in phosphate buffer, 0.1 M, pH 7.4, scan rate  $5 \text{ mVs}^{-1}$ . B) Calibration curve corresponding to the amperometric responses of the reconstituted GOx/CNTs (25 nm) electrode (at  $E = 0.45 \text{ V}$ ) in the presence of different concentrations of glucose. C) Calibration curves corresponding to the amperometric responses (at  $E = 0.45 \text{ V}$ ) of reconstituted GOx/CNTs electrodes in the presence of variable concentrations of glucose and different CNT lengths as electrical connector units: a) about 25 nm SWCNTs, b) about 50 nm SWCNTs, c) about 100 nm SWCNTs, d) about 150 nm SWCNTs. With permission to Patolsky et al. (2004).



## 6. Conclusions and future perspectives

SWCNTs vertical alignment has been demonstrated as a powerful tool for biosensing taking advantage of peculiar properties of carbon nanotubes, their chemistry and straightforward integration with biological environments. Anyway some fabrication features (need of a bridge molecule and coupling efficiency) limits the widespread application of the bidimensional strategy of materials modification.

In such direction, carbon nanotubes based electrodes should address industrial application by the realization of 3D modified materials that can increase active sites number by a bulk doping of materials or eliminate the strong dependence from commonly used noble metals based electrodes. Small quantities of carbon nanotubes could be necessary to realize conductive materials from insulating samples as it is already shown for available synthetic polymers MacDonald et al. (2005): a low degree of doping is needed in order to maintain unchanged wanted bulk properties of starting material such as biocompatibility or stiffness. In such cases, CNTs are suited for biocompatible doped materials since a low level of doping is needed with respect to commonly used fillers like graphite, metals or conductive polymeric structures particles. Also the ability of nanotubes to align following an applied external field creating an electronic percolation path would probably enhance the conductivity of doped materials and in principle further diminish the concentration of dopants. Once realized, carbon nanotube bulk doped biocompatible based devices could be inserted in human body for the realization of drug delivery systems, in vivo biosensors or tissue replacements.

SWCNTs based sensors are actually developed only to measurements in static liquid environments. SWCNTs based sensors integrated in fluidic systems would potentially allow to perform continuous on-line monitoring of multiple-analyte in order to control bioprocesses: for instance combination of glucose and lactate measurements can be related to oxygen-dependent metabolic activity. By enzyme functionalization of forests these measurements can be performed and integrated nanobiosensors can be realized: temporal sequence of dynamic processes and a high-throughput could be achieved. Integrating an electrochemical detector module into microfluidic platforms is preferable because of its inherent portability, the easy of fabrication of the microelectrodes and the lowest costs if compared with other commercial detection systems.

Electrochemical measurements only detect the electrical properties of analyte species undergoing redox reactions, so they are limited to electroactive species. The specific electrode potential can be employed to filter out compounds other than the analyte being detected. In combination with capillary electrophoresis separation, electrochemical detection often provides very good detection limits in microfluidics. Electrochemical detectors for detecting metabolic activity at the extracellular, single-cell level have recently been reviewed Yotter & Wilson (2004) and integration with carbon nanotubes based electrodes is possible.

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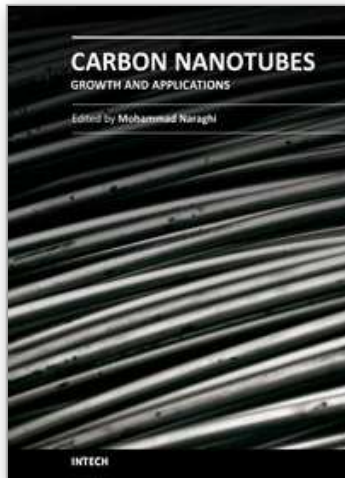
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Carbon Nanotubes are among the strongest, toughest, and most stiff materials found on earth. Moreover, they have remarkable electrical and thermal properties, which make them suitable for many applications including nanocomposites, electronics, and chemical detection devices. This book is the effort of many scientists and researchers all over the world to bring an anthology of recent developments in the field of nanotechnology and more specifically CNTs. In this book you will find:

- Recent developments in the growth of CNTs
- Methods to modify the surfaces of CNTs and decorate their surfaces for specific applications
- Applications of CNTs in biocomposites such as in orthopedic bone cement
- Application of CNTs as chemical sensors
- CNTs for fuelcells
- Health related issues when using CNTs

### **How to reference**

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