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Research review paper

Advances in carbon nanotube based electrochemical sensors for bioanalytical applications

Sandeep Kumar Vashist^{a,b,1}, Dan Zheng^{a,c,1}, Khalid Al-Rubeaan^d, John H.T. Luong^e, Fwu-Shan Sheu^{a,b,*}^a NUSNNI Nanocore, National University of Singapore, T-Lab Level 11, 5A Engineering Drive 1, Singapore 117580^b Department of Electrical and Computer Engineering, National University of Singapore, Engineering Drive 1, Singapore 117576^c Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543^d University Diabetes Center, King Saud University, P. O. Box 18397, Riyadh 11415, Saudi Arabia^e Biotechnology Research Institute, National Research Council Canada, Montreal, Quebec, Canada H4P 2R2

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ABSTRACT

Electrochemical (EC) sensing approaches have exploited the use of carbon nanotubes (CNTs) as electrode materials owing to their unique structures and properties to provide strong electrocatalytic activity with minimal surface fouling. Nanofabrication and device integration technologies have emerged along with significant advances in the synthesis, purification, conjugation and biofunctionalization of CNTs. Such combined efforts have contributed towards the rapid development of CNT-based sensors for a plethora of important analytes with improved detection sensitivity and selectivity. The use of CNTs opens an opportunity for the direct electron transfer between the enzyme and the active electrode area. Of particular interest are also excellent electrocatalytic activities of CNTs on the redox reaction of hydrogen peroxide and nicotinamide adenine dinucleotide, two major by-products of enzymatic reactions. This excellent electrocatalysis holds a promising future for the simple design and implementation of on-site biosensors for oxidases and dehydrogenases with enhanced selectivity. To date, the use of an anti-interference layer or an artificial electron mediator is critically needed to circumvent unwanted endogenous electroactive species. Such interfering species are effectively suppressed by using CNT based electrodes since the oxidation of NADH, thiols, hydrogen peroxide, etc. by CNTs can be performed at low potentials. Nevertheless, the major future challenges for the development of CNT-EC sensors include miniaturization, optimization and simplification of the procedure for fabricating CNT based electrodes with minimal non-specific binding, high sensitivity and rapid response followed by their extensive validation using “real world” samples. A high resistance to electrode fouling and selectivity are the two key pending issues for the application of CNT-based biosensors in clinical chemistry, food quality and control, waste water treatment and bioprocessing.

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* Corresponding author. Department of Electrical and Computer Engineering, National University of Singapore, Engineering Drive 1, Singapore 117576. Tel.: +65 65162857; fax: +65 68725563.

E-mail address: elesfs@nus.edu.sg (F.-S. Sheu).

¹ These authors contributed equally.

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1. Introduction

Electrochemical sensing has been proven as an inexpensive and simple analytical method with remarkable detection sensitivity, reproducibility, and ease of miniaturization. Numerous advantages of CNTs as electrode materials have been attested for analysis of diversified chemicals of food quality, clinical and environmental interest. CNT-EC sensors exhibit low limit of detection (LOD) and fast response due to the signal enhancement provided by high surface area, low overvoltage, and rapid electrode kinetics. A highly thermal conductive, mechanically strong and chemically stable nature of CNTs is very appealing for sensing applications. Their high surface-to-volume ratio is also a definite asset toward the development of biosensing platforms for single-molecule detection.

As hollow cylindrical tubes made up of entire carbon with extremely high aspect ratios (length/diameter), CNTs have one, two or several concentric graphite layers capped by fullerene hemispheres. Besides common single-walled (SWCNTs) and multi-walled CNTs (MWCNTs), double-walled CNTs (Bandow et al., 2001), herringbone (Kiselev et al., 1998), and bamboo CNTs (Saito and Yoshikawa, 1993) have been synthesized. SWCNTs are one dimensional conductor with all electrons moving in an atomic layer having surface atoms. MWCNTs have a complex structure with each carbon layer having different chirality and electronic properties. Detailed information of the CNT structures, dimensions and properties can be found elsewhere (Iijima and Ichihashi, 1993; Iijima, 1991; Delgado et al., 2008; Dresselhaus et al., 2004; Thostenson et al., 2001; Zhu et al., 2002; Merkoci et al., 2005; Luo et al., 2001; Zhao et al., 2004).

This article highlights an overall development of CNT-EC sensors from both research and commercial perspectives. Considering numerous extensive reports and reviews (Agui et al., 2008; Trojanowicz, 2006; Merkoci, 2006; Rivas et al., 2007; Jacobs et al., 2010; Luong et al., 2007) published in the area, the review is limited to the advances in the CNT-EC sensors made in the last decade. Different strategies for preparing CNT based electrodes, a critical component of CNT-EC sensors, are discussed followed by diversified sensing applications and the future challenges in the field of CNT-EC sensors. CNT-EC sensing has progressed with a very fast pace as exemplified by significant advances in the development of sensors (Tables 1–5).

2. Synthesis and functionalization of CNTs

Advances have been made in the areas of CNT synthesis (Kingston and Simard, 2003; Terrones, 2004) and functionalization (Zhao and Stoddart, 2009; Balasubramanian and Burghard, 2005). Arc discharge, laser ablation, and chemical vapor deposition (CVD) are the three main techniques employed for the CNT synthesis. In brief, arc-discharge is costly as it involves the removal of non-nanotube carbon and metal catalysts. Laser ablation can be adapted for fullerene and

SWCNT production by focusing a CO₂ laser beam on the target with a high boiling temperature, e.g., carbon composite doped with catalytic metals. SWCNTs are formed by vaporizing the target in argon at high temperature and conveyed by a gas stream to a collection chamber. The operating temperature, metal species, and the gas flow rate influence the SWCNT diameter. Nevertheless, large-scale productions remain a critical issue with this method despite high homogeneity of SWCNTs produced. CVD uses hydrocarbon vapor which is thermally decomposed using a metal catalyst to form a film or support the particle growth. The CNT growth is governed by the type of hydrocarbon and/or catalyst and growth temperature. CVD provides the synthesis of aligned CNTs as the location can be controlled. Thus, the CVD method is widely used for the commercial preparation of CNTs. Regardless of the method of synthesis, metal impurities remain in the sample and affect the CNT properties. Even after extensive purification, it is still very difficult and costly to obtain CNTs with 99.9% purity. The electrocatalytic behavior of CNTs is unclear and somewhat controversial. At first, electrocatalysis of CNTs is attributed to edge-plane like sites, occurring at the nanotube open ends (Banks et al., 2004, 2005). Further evidence, however, later points out that metal impurities arising from the CVD nanotubes fabrication process might play an important role in the electrocatalytic property of CNTs (Banks et al., 2006; Sljukic et al., 2006).

CNTs can be functionalized with different chemical groups (Balasubramanian and Burghard, 2005; Zhao and Stoddart, 2009) using covalent and non-covalent procedures. Functionalized CNTs are then conjugated to different recognition molecules for bioanalytical applications. Various target analytes can be oxidized by CNTs at low potentials with minimal surface fouling, an appealing feature for the development of sensors with high selectivity and reusability.

Noncovalent functionalization of CNTs is essential to preserve the sp² nanotube structure and thus their important electronic characteristics. The bifunctional molecule, 1-pyrenebutanoic acid, succinimidyl ester is irreversibly absorbed to SWCNTs as the pyrenyl group interacts strongly with the hydrophobic surfaces of the SWCNTs due to π -stacking. The succinimidyl ester groups are highly reactive to nucleophilic substitution with the amines on the surface of most proteins, resulting in the formation of an amide bond. As an example, glucose oxidase (GOx) can be immobilized via noncovalent functionalization of SWCNTs deposited on a silicon wafer to form a sensitive glucose sensor (Besteman et al., 2003).

In order to covalently attach a biomolecule to CNTs, the formation of functional groups on CNTs is a prerequisite. The carboxylic acid group is widely used because it is easily formed on CNTs via oxidizing treatment. This treatment also creates several functional groups such as carbonyl, carboxyl and hydroxyl at the defect sites of the outer graphene sheet. Further treatment with perchloric acid (HClO₄) or potassium permanganate (KMnO₄) will convert all of these groups into carboxylic acids. The carboxylates can be used to link to the

Table 1
Detection of glucose.

CNT modified electrode used	Detection range (LOD)	Sensitivity	Reference
GOx immobilized on a hybrid film of AgNPs/CNTs/Chitosan	0.5–50 μM (LOD 0.1 μM)	135.9 $\mu\text{A mM}^{-1}$	Lin et al. (2009a)
GOx bound to ZnO NPs/MWCNTs	0.1–16 mM	12.5 $\text{mA M}^{-1} \text{cm}^{-2}$ (with 0.5 U GOx)	Wang et al. (2009b)
	0.02–6.0 mM (LOD 250 nM)	50.2 $\text{mA M}^{-1} \text{cm}^{-2}$ (with 2 U GOx)	
Cu NPs in a self-assembled CNT film	50 μM –1.8 mM (LOD 0.1 μM)	602.04 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Li et al. (2009a,b)
Co-deposition of Pd–GOx on a Nafion-solubilized CNT film	0.15–12 mM (LOD 0.15 mM)	N.M.*	Lim et al. (2005)
GOx adsorption on Au and Pt NP modified self-assembled CNT electrode	0.5–17.5 mM (LOD 0.4 mM)	N.M.*	Chu et al. (2007)
A mixture of GOx and a CNTs film sandwiched with 10 nm-thick PPFs	0.025–2.2 mM (LOD 6 μM)	42 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Muguruma et al. (2008)
Immobilization of <i>Pseudomonas putida</i> DSM 50026 cells on CNT modified carbon paste electrodes using a redox osmium (Os) polymer	0.05–2.0 mM	131.32 $\text{nA mM}^{-1} \text{cm}^{-2}$	Timur et al. (2007)
Ultrasonic-electrodeposition of bimetallic PtM (M–Ru, Pd and Au) NPs on a CNT-ionic liquid composite film	0.2–15 mM (LOD 0.05 mM)	10.7 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Xiao et al. (2009)
Incorporation of a CNTs dopant and a biocatalyst within an electropolymerized PPy film	4 mM–50 mM (LOD 0.2 mM)	2.33 nA mM^{-1}	Wang and Musameh (2005)
Incorporation of GOx into the colloidal Au–CNT composite matrix	0.05–1 mM	2.6 mA M^{-1}	Manso et al. (2007)
GOx bound to ferrocene-modified MWCNT nanocomposites GOx/MWCNT–Fc/Chitosan	12 μM –3.8 mM (LOD 3.0 μM)	25 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Qiu et al. (2009)
Low-density discrete flower-like Au nanoparticles (AuNPs) or continuous AuNP films are electrodeposited on the SWCNT–thin-film filtering membrane electrode (FME)	N.M.*	N.M.*	Hu et al. (2010)
GOx immobilized on a 3,39-diaminobenzidine (DAB)-electropolymerized CNT electrode	1×10^{-4} – 2×10^{-3} M	N.M.*	Loh et al. (2004)
MWCNT-filled nanofibrous membrane electrospun from poly(acrylonitrile-co-acrylic acid) (PANCAA) on a Pt electrode	0.67–7 mM (LOD 0.67 mM)	0.18 $\mu\text{A mM}^{-1}$	Wang et al. (2009c)
SWCNT–GOx-silica matrix on a screen-printed carbon electrode (SPCE) on toray paper	(LOD 40 mM)	N.M.*	Ivnitski et al. (2008)
		N.M.*	
Cellulose-MWCNT–GOx on GCE using 1-ethyl-3-methylimidazolium acetate as solvent	0.05–1.0 mM (LOD 0.46 mM)	0.46 $\mu\text{A mM}^{-1}$	Wu et al. (2009)
PtNP–chitosan–MWCNT–GOx– SiO_2 sol–gel on GCE	1 μM –23 mM (LOD 1 μM)	58.9 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Zou et al. (2008)
CS–GOx–CdS NPs on aligned CNT–PtNP electrodes	400 μM –21.2 mM (LOD 46.8 μM)	45 $\mu\text{A nM}^{-1}$	Yang et al. (2008a)
GOx–Nafion–SWCNTs on GCE	0.5–6 mM (LOD 6 μM)	1.06 $\mu\text{A mM}^{-1}$	Liu et al. (2008a)
GOx immobilized nitrogen-doped carbon nanotubes (CN–MWNT) modified GCE	0.02–1.02 mM (LOD 10 μM)	13.0 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Deng et al. (2009)
GOx bounded self assembled amine-terminated ionic liquid NH_2 –IL on Au NPs electrodeposited NH_2 –IL functionalized SWCNT–GCE	2.0×10^{-6} – 5.0×10^{-5} M (LOD 0.8 μM)	0.49 $\mu\text{A } \mu\text{M}^{-1}$	Gao et al. (2009)
GOx–HRP in a PPy film on a SWCNT/Au electrode	0.030–2.43 mM (LOD 30 μM)	$7.01 \pm 0.18 \mu\text{A mM}^{-1} \text{cm}^{-2}$	Zhu et al. (2007a)
Thionine cross-linked MWCNT and Au NP multilayer functionalized indium-doped tin oxide (ITO) electrode modified with glucose dehydrogenase (GDH)	1 μM –3.25 mM (LOD 0.7 μM)	18.5 $\mu\text{A mM}^{-1}$	Deng et al. (2008)
GOx–HRP in Nafion on MWCNTs/GCE	0.025–0.4 mM (LOD 0.5 μM)	80.5 $\text{mA M}^{-1} \text{cm}^{-2}$	Yao and Shiu (2008)
GOx in Nafion on MWCNTs–AuNPs/GCE	0.05–22 mM (LOD 20 μM)	0.4 $\mu\text{A mM}^{-1}$	Rakhi et al. (2009)
GOx–BSA–glutaraldehyde (GA)–CNTs on carbon film cylindrical electrodes	0.05–0.9 mM (LOD 5 μM)	289 $\mu\text{A cm}^{-2} \text{mM}^{-1}$ (–0.15 V, vs. SCE)	Gouveia-Caridade et al. (2008)
GOx–poly(toluidine blue O) film on CNTs/GCE	1–7 mM (LOD 1 mM)	14.5 $\text{mA M}^{-1} \text{cm}^{-2}$	Yao and Shiu (2007)
GOx–cubic Prussian Blue–SWCNTs in chitosan on GCE	0.5–13.5 mM (LOD 5 μM)	0.44 $\mu\text{A mM}^{-1}$	Zhang et al. (2009a)
GOx–poly(ethylene imine)/poly(acrylic acid) (PEI/PAA)–CNT–ferrocene derivatives on GCE	10–80 mM (LOD 10 mM with PEI) 10–80 mM (LOD 10 mM with PAA)	N.M.*	Yan et al., 2008
		N.M.*	
(11-pyrrolyl-1-yl-undecyl) triethylammonium tetrafluoroborate–SWCNT–GOx deposited Pt disks electropolymerized in LiClO_4 solution	40–4500 μM	130 $\text{mA M}^{-1} \text{cm}^{-2}$	Cosnier et al. (2008)
GOx linked to networks of SWCNTs decorated with Au-coated Pd nanocubes	10 μM –50 mM (LOD 1.3 μM)	5.2 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Claussen et al. (2009)
PtNPs inserting in a CNTs array with GOx	0.16–11.5 mM (LOD 55 μM)	6.15 $\mu\text{A mM}^{-1}$	Wen et al. (2009a)
GOx in Nafion with PtNPs–aligned MWCNTs on an Au film	10 μM –7 mM (LOD 8.9 μM)	N.M.*	Zhao et al. (2007)
GOx–PtNPCNT–alumina-coated silica/GCE	50 μM –10.5 mM (LOD 6.18 μM)	113.13 $\text{mA M}^{-1} \text{cm}^{-2}$	Tsai and Tsai (2009)
Cu nanoclusters–Nafion–MWCNTs on GCE	7.0×10^{-7} – 3.5×10^{-3} M (LOD 210 nM)	17.76 $\mu\text{A mM}^{-1}$	Kang et al. (2007)
PdNP–SWCNT hybrid nanostructures on GCE	0.5–17 mM (LOD 200 nM)	160 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Meng et al. (2009a)
Cu_2O /MWCNT nanocomposites in Nafion on GCE	0.05–10 mM (LOD 50 nM)	6.53 $\mu\text{A } \mu\text{M}^{-1}$	Zhang et al. (2009b)
GOx–PtNP–CNT–titania nanotube (NT) arrays	0.006–1.5 mM (LOD 3 μM)	0.24 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Pang et al. (2009)
Pyranose oxidase (POx)–CNT paste electrode	0.2–30 μM	0.12 $\mu\text{A mM}^{-1} \text{cm}^{-2}$	Odaci et al. (2008)

*N.M.—Not Mentioned.

Table 2
Detection of neurotransmitters/neurochemicals.

Analyte detected	CNT modified electrode used	Detection range	Sensitivity	Reference
Acetylcholine	Acetylcholinesterase (AChE) immobilized on SiO ₂ NPs deposited on the self-assembled SWCNTs	10 μ M–10 mM (LOD 10 nM)	378.2 mA decade ^{−1}	Xue and Cui (2008)
Epinephrine	CNT paste electrode modified with 2-(4-oxo-3-phenyl-3,4-dihydro-quinazolinyl)-N'-phenyl-hydrazinecarbothioamide	5×10^{-8} – 5.5×10^{-4} M (LOD 9.4 nM)	N.M.*	Beitollahi et al. (2008b)
	PMB functionalized MWCNT modified GCE	2.5 μ M–0.76 mM (LOD 69.6 μ M in 0.2 mM AA)	19.77 μ A mM ^{−1} cm ^{−2}	Yogeswaran and Chen (2008)
	SWCNTs electrodeposited on stainless steel wire	2–100 mM (LOD 2 μ M)	28.1 A M ^{−1} cm ^{−2}	Valentini et al. (2007a)
	Film MWCNTs-PNDGA-chitosan on SPCE	0.03–1.28 mM (LOD 30 μ M)	1964 μ A μ M ^{−1} cm ^{−2}	Li et al. (2009a)
	In situ electropolymerization of BCB-MWCNTs on GCE	50 nM–10 μ M (LOD 10 nM)	2.8 μ A μ M ^{−1}	Yi et al. (2008)
	EBNBH modified CNT paste electrode	0.7–1200 μ M (LOD 0.2 μ M)	0.0289 μ A μ M ^{−1}	Beitollahi et al. (2008a)
	Hematoxylin electrodeposited on MWCNT/GCE	0.2–78.3 μ M (LOD 0.024 μ M)	0.048 μ A μ M ^{−1}	Zare and Nasirizadeh (2010)
Norepinephrine	Film MWCNTs-PNDGACHi on SPCE	0.78–31.80 mM (LOD 780 μ M)	3067 μ A μ M ^{−1} cm ^{−2}	Li et al. (2009a)
Ascorbic acid	SPCE modified with polyacrylic acid-coated MWCNTs	0–10 μ M (LOD 0.131 μ M)	8.295 μ A μ M ^{−1}	Huang et al. (2010)
	Nanohybrid modified electrode composed of MWCNT-silica network-AuNPs	1–5 mM	8.59 μ A mM ^{−1}	Ragupathy et al. (2010)
	Electro-copolymerization of OPPY-SWCNTs on GCE	20 μ M–1 mM (LOD 4.6 μ M)	N.M.*	Li et al. (2007)
	Cobalt(II)-nitrosalophen-Nafion-MWCNTs on CPE	0.5 μ M–0.1 mM (LOD 0.1 μ M)	0.1161 μ A μ M ^{−1}	Shahrokhian and Zare-Mehrjardi (2007a)
	Hematoxylin electrodeposited on MWCNT/GCE	133.5–800.0 μ M	0.0059 μ A μ M ^{−1}	Zare and Nasirizadeh (2010)
	[PDDA/MWCNTs wrapped with polystyrene sulfonate] ₅ on graphite electrode	50 μ M–1 mM (LOD 0.5 μ M)	2.2745 μ A μ M ^{−1}	Manjunatha et al. (2010)
	SPCE modified with polyacrylic acid-coated MWCNTs	100–1000 μ M (LOD 49.8 μ M)	0.026 μ A μ M ^{−1}	Huang et al. (2010)
Dopamine	Covalent attachment of SWCNTs on the interior surface of a conical glass micropore electrode (GME); Nafion-treated	9.9×10^{-7} – 3.0×10^{-4} M (LOD 4.2×10^{-7} M)	60.4 nA mM ^{−1}	Cao et al. (2010)
	Tyrosinase-SWCNT-PPy composite	5–50 μ M (LOD 5 μ M)	467 mA M ^{−1} cm ^{−2}	Min and Yoo (2009)
		20 μ M–0.2 mM (LOD 3.75 μ M)	0.024 μ A mM ^{−1}	Zheng et al. (2008)
	2,2'-[1,2-ethanediybis(nitriloethylidene)]-bis-hydroquinone modified CNTs-CPE	0.1–900 μ M (LOD 0.09 μ M)	0.1372 μ A μ M ^{−1}	Mazloun-Ardakani et al. (2009)
	RuO ₂ modified vertically aligned MWCNT electrode	0.6 μ M–3.6 mM (LOD 60 nM)	83.8 μ A mM ^{−1}	Jiang and Zhang (2009)
	Electro-copolymerization of OPPY-SWCNTs on GCE	1.0–50 μ M (LOD 0.38 μ M)	N.M.*	Li et al. (2007)
	Electro-copolymerization of OPPY-MWCNTs on GCE	2.5 nM–5.0 μ M (LOD 0.75 μ M)	N.M.*	Wen et al. (2009a)
	Thionine-Nafion supported MWCNT modified GCE	0.10–80 μ M (LOD 0.08 μ M)	0.0201 μ A μ M ^{−1}	Shahrokhian and Zare-Mehrjardi (2007b)
	PMB functionalized MWCNT modified GCE	2.5 μ M–0.76 mM (LOD 67 μ M in 0.2 mM AA)	22.13 μ A mM ^{−1} cm ^{−2}	Yogeswaran and Chen (2008)
	PNR functionalized MWCNT modified GCE	0.075–0.2 mM (LOD 0.1 mM)	0.146 μ A μ M ^{−1}	Yogeswaran and Chen (2007)
	Layer-by-Layer deposition SWCNTs and positively charged cetylpyridinium bromide onto GCE	4.0 μ M–0.12 mM (LOD 0.6 μ M)	0.073 μ A μ M ^{−1}	Zhang et al. (2007)
	Molecularly imprinted polymers, MWCNTs on GCE	0.5 μ M–0.2 mM (LOD 0.5 μ M)	N.M.*	Kan et al. (2008)
	Poly(acrylic acid)-MWCNTs on GCE	40 nM–3 μ M (LOD 20 nM)	N.M.*	Liu et al. (2007)
	Poly(3-methylthiophene), MWCNTs, Nafion on GCE	0.02–0.10 μ M	7.765 μ A μ M ^{−1}	Wang et al. (2006)
		0.10–1.0 μ M	3.257 μ A μ M ^{−1}	
		1.0–6.0 μ M (LOD 5 nM)	1.995 μ A μ M ^{−1}	
	Laccase-MWCNT modified GCE	1.0–30.0 μ M (LOD 0.4 μ M)	0.61 μ A μ M ^{−1}	Xiang et al. (2007)
	Tyrosinase-MWCNT-Nafion on GCE	5–23 μ M (LOD 0.5 μ M)	12 μ A mM ^{−1}	Tsai and Chiu (2007)
	Borinic acid functionalized MWCNT modified GCE	0.05–500 μ M (LOD below 0.05 μ M)	N.M.*	Wu et al. (2007)
	PABA-SWCNT-ssDNA on Au electrode	1–10 nM (LOD 1.5 nM)	N.M.*	Ali et al. (2007)
	SWCNTcoated carbon fiber microelectrodes	N.M.* (LOD 250 nM)	N.M.*	Swamy and Venton (2007)
	Gel formation with IL of imidazolium ions with SWCNTs used as an electrode	0.1–12 μ M (LOD 60 nM)	N.M.*	Sun et al., 2009
	[PDDA/MWCNTs wrapped with polystyrene sulfonate] ₅ on graphite electrode	50–350 μ M (LOD 0.15 μ M)	12.3702 μ A μ M ^{−1}	Manjunatha et al. (2010)
Uric acid	Acid functionalized MWCNT-GCE	3–200 μ M (LOD 0.8 μ M)	N.M.*	Alothman et al. (2010)
	MWCNTs polymerized with a layer of molecularly imprinted polymer (MIP) made from poly-methacrylic acid (PMAA)	80–500 μ M	11.03 mA M ^{−1} cm ^{−2}	Chen et al. (2010)
	2,2'-[1,2-ethanediybis(nitriloethylidene)]-bis-hydroquinone modified CNT-paste electrode	20–650 μ M (LOD 15 μ M)	0.027 μ A μ M ^{−1}	Mazloun-Ardakani et al. (2009)
	Electro-copolymerization of OPPY-SWCNTs on GCE	2 μ M–0.1 mM (LOD 0.74 μ M)	N.M.*	Li et al. (2007)
	Layer-by-layer deposition SWCNTs and positively charged cetylpyridinium bromide onto GCE	2 μ M–90 mM (LOD 7 μ M)	0.117 μ A μ M ^{−1}	Zhang et al. (2007)
	Poly(acrylic acid)-MWCNTs on GCE	0.3–10 μ M (LOD 110 nM)	N.M.*	Liu et al. (2007)

Table 2 (continued)

Analyte detected	CNT modified electrode used	Detection range	Sensitivity	Reference
	GCE modified with MWCNTs dispersed in pLys	10 μ M–0.1 mM (LOD 17 μ M)	$(98 \pm 0.2) \times 10^4 \mu\text{A M}^{-1}$ in 1.0 mM AA	Rodríguez et al. (2008)
	Cobalt(II)-nitrosalophen-Nafion-MWCNTs on CPE	0.1 μ M–0.1 mM (LOD 0.06 μ M)	0.1598 $\mu\text{A } \mu\text{M}^{-1}$	Shahrokhian and Zare-Mehrjardi (2007a)
	SWCNT-inlaying ultrathin CPE	0.1–8.0 μ M 8.0–0.1 mM (LOD 0.08 μ M)	18.26 $\mu\text{A nM}^{-1}$ 22.80 $\mu\text{A nM}^{-1}$	Wang et al. (2008)
	2,2'-[1,2-ethanediylbis(nitriloethylidyne)]-bis-hydroquinone modified CNT paste electrode	25–750 μ M (LOD 8.8 μ M)	0.0147 $\mu\text{A } \mu\text{M}^{-1}$	Beitollahi et al. (2008a)
	Hematoxylin electrodeposited on MWCNT/GCE	26.7–240.0 μ M	0.047 $\mu\text{A } \mu\text{M}^{-1}$	Zare and Nasirizadeh, 2010
	[PDDA/MWCNTs wrapped with polystyrene sulfonate] ₅ on graphite electrode	50–800 μ M (LOD 0.8 μ M)	2.5306 $\mu\text{A } \mu\text{M}^{-1}$	Manjunatha et al. (2010)
Serotonin	SPCE modified with polyacrylic acid-coated MWCNTs	0–30 μ M (LOD 0.458 μ M)	8.295 $\mu\text{A } \mu\text{M}^{-1}$	Huang et al. (2010)
	SWCNT coated carbon fiber microelectrodes	N.M.* (LOD 130 nM)	N.M.*	Swamy and Venton (2007)
Xanthine	Gel formation with IL of imidazolium ions with SWCNTs used as an electrode	20 nM–7 μ M (LOD 80 nM)	N.M.*	Sun et al. (2009)
	Functional SWCNT film electrode constructed on the surface of inlaying ultra-thin carbon paste electrode (IUTCPE)	2.0×10^{-7} – 1.0×10^{-4} M (LOD 1.46×10^{-7} M)	$1.255 \times 10^{-8} \mu\text{A M}^{-1}$	Wang et al. (2008)
	Xanthine oxidase (XOD) bound to MWCNT modified glassy carbon (GC) electrode	0.2–10 μ M (LOD 0.1 μ M)	N.M.*	Gao et al. (2009)
Hypoxanthine	Functional SWCNT film electrode constructed on the surface of inlaying ultra-thin carbon paste electrode (IUTCPE)	0.8–20 μ M 20–100 μ M (LOD 0.5 μ M)	32.67 $\mu\text{A nM}^{-1}$ 13.31 $\mu\text{A nM}^{-1}$	Wang et al. (2008)

*N.M.—Not Mentioned.

amino groups of biomolecules or proteins using a well-known carbodiimide procedure. In brief, the reaction between $\text{N}-\text{C}-\text{N}$ of the carbodiimide with the carboxyl group of CNTs will form a highly reactive *o*-acylisourea derivative with an extremely short life. This active species will react with the amino group of a biomolecule (enzyme, protein, etc.) to form an amide bond. Carbodiimides are zero-length crosslinking agents as no additional chemical structure is introduced between CNTs and biomolecules. In some cases, the activity of the immobilized biomolecules may be affected due to steric hindrance by covalent binding. This procedure is often used to crosslink biomolecules such as proteins–proteins, peptides–proteins, nucleotides–proteins, and also a biomolecule to a substrate. The water-soluble carbodiimide (also EDAC or EDCI, acronyms for 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) and Sulfo-NHS (N-hydroxysulfosuccinimide) are widely used for this coupling reaction. The advantage of adding sulfo-NHS to EDC reactions is to increase the stability of the active intermediate and the overall coupling efficiency compare to using EDC alone. The protein is able to covalently bind to the activated CNTs by nucleophilic attacks of amino groups on COONHS active groups. Further information of this coupling procedure can be found elsewhere (Anjaneyulu and Staros, 1987; Thelen and Deuticke, 1988; Grabarek and Gergely, 1990). As an example, carboxylic groups are introduced onto CNTs by oxidation and bound to the amino groups of oligonucleotide by amide bonds (Berti et al., 2009). The DNA probe is initially mixed with EDC to activate the DNA strands while 1-methylimidazole (MIA) is added to stabilize the activated EDC molecules. The MIA-activated probe DNA strands are bound to the sensor via their phosphate groups, which bind covalently to the amine groups of treated-MWCNTs (Tam et al., 2009). Covalent immobilization of anti-mouse IgG on a CNT array results in an immunosensor for mouse immunoglobulin G (Yun et al., 2007).

3. Preparation of CNT based electrodes

CNT based electrodes exhibit excellent electrocatalysis, mainly contributed by the activity of edge-plane-like graphite sites at the CNT ends (Nugent et al., 2001) and/or the metal catalyst. Perhaps, the simplest way is to coat the electrode surface with a CNT suspension. Hence, CNT based electrodes are often fabricated by the dispersion of CNTs in solvents and binding of CNTs with metallic nanoparticles/

polymers. The subject of CNT based composite electrodes has been extensively reviewed (Spitalsky et al., 2010; Sahoo et al., 2010; Chu et al., 2010; Capek, 2009; Luong et al., 2007).

3.1. Dispersion of CNTs in solvents

The modification of CNTs with β -Cyclodextrin (β -CD) is simple and effective as the prolonged heating, filtration and washing conditions, which can damage CNTs, are not required (Chen et al., 2001). CNTs are simply dispersed in a β -CD solution with sonication, resulting in a 2 mg/mL suspension (He et al., 2006). An aliquot of this suspension is dropped on a glassy carbon electrode (GCE) followed by air drying to form a CNT modified electrode. Alternatively, the electrode can be prepared by mixing CNTs, *N,N*-dimethylformamide (DMF) and β -CD to form a CNT dispersion (Shen and Wang, 2009). Another approach is based on chitosan (CS), a natural biopolymer with high permeability to water and good adhesion. A CS/CNT modified electrode is fabricated by coating the electrode with a CS-acetic acid solution or a CNT-CS suspension (Zhang et al., 2010c; Liu et al., 2008a). Alternatively, Nafion, a perfluorosulfonated polymer, is widely used to disperse acid treated CNTs due to its unique ionic properties (Wang and Musameh, 2003). It disperses nitric acid treated CNTs to form a stable and homogenous CNT/Nafion composite (Gong et al., 2004). Dicyetyl phosphate (DCP) can also be used to prepare CNT based electrodes. In this procedure, MWCNTs and DCP are dispersed in deionized water by ultrasonication, resulting in a 0.5 mg/mL homogeneous suspension. GCE is then coated by using the MWCNT-DCP suspension followed by air-drying at room temperature (Lü, 2004).

3.2. Binding of CNTs with metallic nanoparticles

Electrodeposition of platinum nanoparticles (PtNPs) on CNTs is usually carried out at -0.25 V in an electroplating bath containing H_2PtCl_6 and H_2SO_4 under gentle stirring (Chu et al., 2007). CNTs with PtNPs are obtained by reducing $\text{H}_2\text{Pt}(\text{NO}_2)_2\text{SO}_4$ with NaBH_4 in the dark with constant stirring (Guzmán et al., 2009). Alternatively, CNT based electrodes can be immersed in a solution of K_2PtCl_4 and K_2SO_4 . The electrooxidation of PtCl_4^{2-} is conducted on CNTs at 0.3 to 1.3 V until no distinct anodic peaks are observable. The CNT electrode is removed and electroreduced at -0.25 V in 0.1 M H_2SO_4 for 2 min,

Table 3
Detection of proteins.

Analyte detected	CNT modified electrode used	Detection range	Sensitivity	Reference
Arginine	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 5×10^{-6} M	7.8×10^4 nA M ⁻¹	Dong et al. (2008)
Tryptophan	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 1×10^{-6} M	1.1×10^5 nA M ⁻¹	Dong et al. (2008)
Histidine	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 1×10^{-6} M	1.7×10^5 nA M ⁻¹	Dong et al. (2008)
Threonine	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 1×10^{-6} M	1.3×10^5 nA M ⁻¹	Dong et al. (2008)
Serine	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 5×10^{-6} M	5.4×10^4 nA M ⁻¹	Dong et al. (2008)
Tyrosine	MWCNT-Cu ₂ O paste electrode	1×10^{-4} – 5×10^{-6} M	8.7×10^4 nA M ⁻¹	Dong et al. (2008)
Glutamate	Glutamate dehydrogenase (GLDH) immobilized on SWCNTs-thionine mediator	0.5–400 μM (LOD 0.1 μM)	137.3 ± 15.7 μA mM ⁻¹ cm ⁻²	Meng et al. (2009a)
	Self-assembling glutamate dehydrogenase (GLDH) and poly(amidoamine) dendrimer-encapsulated platinum nanoparticles (Pt-PAMAM) onto MWCNTs	0.2–250 μM	433 μA mM ⁻¹ cm ²	Tang et al. (2007)
	MWCNTs, chitosan, redox mediator meldola's blue (MDB) and glutamate dehydrogenase (GLDH) composite	25–250 μM (LOD 2 μM)	0.71 ± 0.08 nA μM ⁻¹	Chakraborty and Raj, 2007
L-Cysteine	Pt deposited on CNT modified graphite electrode	0.5 μM–0.1 mM (LOD 0.3 μM)	0.807 nA μM ⁻¹	Fei et al. (2005)
Homocysteine	Nafion-CNT modified glassy carbon electrode	0.1–60 μM (LOD 0.06 μM)	N.M.*	Gong et al. (2004)
Human IgG	Anti-human IgG adsorbed on SWCNTs-FET	0–4 mg L ⁻¹ (LOD 0.5 mg L ⁻¹)	–1.5 nA (mg L ⁻¹) ⁻¹	Cid et al. (2008)
Mouse IgG	Anti-mouse IgG covalent bound to carboxyl functionalized CNTs	0.2–100 μg mL ⁻¹ (LOD 200 ng mL ⁻¹)	N.M.*	Yun et al. (2007)
IgG	Protein G adsorbed on network SWCNTs-FET on SiO ₂	(LOD 8.8 nM)	N.M.*	Villamizar et al. (2009a)
	CNTs-FET, IgG antibody adsorbed, secondary antibody binds, caused pH change	0.4–400 ng mL ⁻¹ (LOD 0.4 ng mL ⁻¹)	N.M.*	Lu et al. (2009)
	Antibody fragment on SWCNTs-FET	1–100 pg mL ⁻¹ (LOD 7 fM)	N.M.*	Kim et al. (2008)
IgE	Aptamer on SWCNTs-FET	250 pM–160 nM (LOD 250 pM)	N.M.*	Maehashi et al. (2009)
Rabbit IgG	SWCNTs in polystyrene, plasma activated, sandwich assay HRP-Ab	3–100 ng mL ⁻¹ (LOD 21 pM)	N.M.*	Fernández-Sánchez et al. (2009)
Pig serum albumin	IgG antibodies adsorbed on SWCNTs-FET	N.M.* (LOD 5 nM)	N.M.*	Abe et al. (2007)
BSA	Self-assembly of oxidative SWCNTs on Au	0.1–1.2 mM	3.89 μA μM ⁻¹ (24 h assembly time) 1.46 μA μM ⁻¹ (3 h assembly time)	Chen and Huang (2009)
Streptavidin	Avidin-MWCNT modified electrode	15 nM–7.5 μM (LOD 1.5 nM)	N.M.*	Fang et al. (2008)
	Biotinylated SWCNTs-FET coated with PEI/PEG	N.M.*	50 nM	Hu et al. (2008)
	Supported lipid bilayers over single-walled carbon nanotube transistors	N.M.* (LOD 5 μM)	N.M.*	Zhou et al. (2007)
Insulin	Ruthenium oxide (RuOx) deposited onto a CNT layer	10–800 nM (LOD 1 nM)	541 nA μM ⁻¹	Wang et al. (2007)
	CNTs/chitosan/cobalt hexacyanoferrate NPs composite	0.1–3 μM (LOD 40 nM)	N.M.*	Qu et al. (2006)
	MWCNTs-dihydropuran polymer on GCE	1–10 μM (1 mm GCE)		
0–1000 μM (3 mm GCE)	0.33 ± 0.08 nA μM ⁻¹	Snider et al. (2008)		
hCG	Anti-hCG bound modified electrode; MWCNT-chitosan (CS) modified glassy carbon electrode with incorporated toluidine blue (TB) and hemoglobin (Hb) followed by electrostatic adsorption of a conducting AuNPs film.	0.8–500 mIU mL ⁻¹ (LOD 0.3 mIU mL ⁻¹)	0.1032 μA mL mIU ⁻¹	Li et al. (2008)
CRP	Anti-HCG bound to MWCNT-modified screen-printed electrodes via protein A attached covalently to MWCNTs	0.5–200 ng mL ⁻¹ (LOD 0.5 ng mL ⁻¹)	N.M.*	Buch and Rishpon (2008)
PSA	SWCNT forest bound anti-PSA	0.04–5 ng mL ⁻¹ (LOD 40 pg mL ⁻¹)	2864 (photons) mL ng ⁻¹	Sardesai et al. (2009)
	CNTs-FET with anti-PSA with spacers in between antibodies	0.25–1 ng mL ⁻¹ (LOD 0.25 ng mL ⁻¹)	N.M.*	Okuno et al. (2007)
PSA-ACT	CNTs-FET functionalized with a solution containing various linker-to-spacer ratios	1–100 ng mL ⁻¹ (CNT-FET modified with a 1:3 ratio of linker-to-spacer) (LOD 1 ng mL ⁻¹)	N.M.*	Kim et al. (2009)
CEA	Monoclonal anti-CEA bound covalently to PEI wrapped MWCNT screen-printed electrode	5×10^{-12} – 5×10^{-7} g mL ⁻¹ (LOD 1×10^{-12} g mL ⁻¹)	N.M.*	Viswanathan et al. (2009)
A-fetoprotein	Glassy carbon electrode (GCE) modified with Au NPs and CNTs doped chitosan	1–55 ng mL ⁻¹ (LOD 0.6 ng mL ⁻¹)	4.5×10^{-2} μA mL ng ⁻¹	Lin et al. (2009a)
	Anti-AFP/AuNP/Thi/Nafion-MWCNT modified electrode	0.5–200 ng mL ⁻¹ (LOD 0.26 ng mL ⁻¹)	2.09 μA mL ng ⁻¹ , 0.08 μA mL ng ⁻¹	Su et al. (2009)
IL-6	SWCNT forests modified electrodes	40–150 pg mL ⁻¹ (LOD 30 pg mL ⁻¹)	3 nA cm ⁻² (pg mL ⁻¹) ⁻¹	Munge et al. (2009)

*N.M.—Not Mentioned.

resulting in the deposition of PtNPs on CNTs (Fei et al., 2005). Gold nanoparticles (AuNPs) are electrochemically deposited onto CNTs from a solution of HAuCl_4 by cycling the potential between 1.0 and 0.0 V vs. saturated calomel electrode (Ragupathy et al., 2010). CNTs can be modified with AuNPs by mixing CNTs with a 0.01% HAuCl_4 solution followed by adding 1% trisodium citrate to the stirred boiling solution of CNTs and HAuCl_4 (Lin et al., 2009a). A CNT/copper (Cu) paste electrode is prepared by mixing mineral oil, CNTs and Cu nanopowder, followed by filling the paste material into a piece of fused silica capillary together with a copper wire (Valentini et al., 2007a). Copper nanoclusters are electrochemically deposited on CNT electrodes by applying a potential of -1.0 V in a degassed Na_2SO_4 and CuSO_4 solution. Cu nanoparticles (CuNPs) can also be prepared by reducing copper dodecyl sulfate using sodium borohydride, followed by binding with SWCNTs (Male et al., 2004). Silver nanoparticle (AgNP)/CNT/CS composite films are synthesized by adding 1% trisodium citrate to a boiling mixture of CNTs, CS and AgNO_3 (Lin et al., 2009a). AgNP-coated CNTs are also obtained by adding 0.01 M AgNO_3 dropwise to the oxidized CNT-deionized water suspension with continuous stirring at room temperature for 20 h (Gao et al., 2006). A palladium (Pd)-glucose oxidase (GOx) composite is electro-deposited on CNT/GCE or Nafion/CNT/GCE at -0.9 V under gentle stirring (Lim et al., 2005). Of interest is the alignment of CNTs in polymer nanocomposites by absorbing Fe_2O_3 nanomagnetic particles on the CNT surface under an external magnetic field (Aldajah et al., 2009).

3.3. Binding of CNTs with polymer

A polypyrrole (PPy)-CNT-tyrosinase biocomposite film is prepared by electrochemical polymerization (Ozoner et al., 2010). Similarly, a PPy-GOx-MWCNT modified electrode is fabricated by electropolymerization of a mixture of MWCNTs, GOx, and PPy (Wang and Musameh, 2005). A MWCNT/polyaniline (PANI) multilayer film is formed by alternate casting of treated MWCNT-ethanol dispersion and electrodeposition of aniline. The MWCNT-modified electrode is immersed into a mixture of aniline and H_2SO_4 . Thereafter, a PANI film is deposited by recycling the potential between -0.2 and $+1.0$ V for 6 cycles (Qu et al., 2005). An acetonitrile plasma-polymerized film (PPF) can also be deposited by a plasma generator on the enzyme-absorbed CNT surface (Muguruma et al., 2008). A CS/polyvinylimidazole-osmium (PVI-OS)/CNT/lactate oxidase (LOx) network is used to modify an Au electrode functionalized with mercaptopropionic acid (Cui et al., 2007).

MWCNTs can be modified with amine-terminated poly(amidoamine) (G4-NH_4) by dropping EDC and G4-NH_4 on a MWCNT/GCE surface (prepared by evaporation of DMF). The resulting electrode is then covered with a plastic cap and kept for 6 h at room temperature to obtain a polymer-CNT modified electrode (Zhu et al., 2009). CNTs can also be modified by polymer-metallic nanoparticles (Fig. 1). For the preparation of AgNP/poly(trans-3-(3-pyridyl) acrylic acid) (PPAA)/carboxylated MWCNT/GCE, a polymer film is deposited onto a carboxylated MWCNT modified electrode by cyclic voltammetry in 1 mM PPAA (Zhang et al., 2009d). Thereafter, AgNPs are coated on the PPAA/carboxylated MWCNT/GCE composite film by CV at 0.25 V vs. SCE in a 3.5 mM AgNO_3 /0.1 M NaNO_3 solution.

Nanogold (Au_{nano}) can also be deposited on CNTs by dropwise addition of HAuCl_4 solution to a CNT-citric acid suspension at 70°C under vigorous stirring to yield a hybrid suspension (Zhou et al., 2009). The Au_{nano} -CNT suspension is dropped onto the GCE surface containing polyaniline nanofibers (PAN_{nano}) to form an Au_{nano} -CNT/ PAN_{nano} modified electrode. CNT reinforced polymeric matrix nanocomposites are prepared by polymerization of poly(methyl methacrylate) and polystyrene (Etman et al., 2009). This typical procedure includes the admixture of CNTs and the polymers, drying of the mixture and dissolving it with toluene. A uniform suspension of CNTs

(up to 10 mg/mL) can be prepared using carboxymethylcellulose or kappa-carrageenan, which may wrap around CNTs. The strategy based on kappa-carrageenan-CNT network is used for entrapping GOx in a stable manner to form a biosensing scheme for detection of glucose (Hrapovic et al., 2008).

3.4. Other strategies

Clay and ceramic materials are also useful for modification of CNT based electrodes. NiO/Na-montmorillonite (clay) binds to CNTs and is used to modify GCE using a Nafion solution (Hsu et al., 2009). A CNT ceramic composite is prepared by admixing CNTs and silica sol (Zhu et al., 2007). Toluidine blue (Tb) adsorbs on CNTs to improve the dispersion of CNTs in water (Liu et al., 2008b). The Tb-CNT suspension is then dropped on the electrode surface for subsequent modification with horseradish peroxidase. Ionic liquid (IL) modified CNTs are highly resistant towards biomolecular fouling and have high electron transfer kinetics (Xiao et al., 2007). The IL/CNT modified electrode is prepared by adding CNTs to trihexyltetradecylphosphonium bis (trifluoromethylsulfonyl)-imide and dispersing in DMF with ultrasonication (Xiao et al., 2009). The IL-CNT suspension is dropped on the electrode surface for subsequent electrodeposition of metallic nanoparticles.

Ferrocene and its derivatives are widely used as artificial mediators of electron transfer in CNT-EC sensors owing to their relatively low molecular mass and reversible voltammograms (Brown and Luong, 1995; Fernández and Carrero, 2005). NaCNBH_3 is added to a suspension of aminated MWCNT and ferrocenecarboxaldehyde (FcCHO) with stirring for 24 h. The resulting MWCNT-FcCHO nanocomposite is used to modify GCE (Qiu et al., 2009).

4. Biomolecular sensing

CNT-EC sensors have been extensively reported for biomolecular sensing, especially for the detection of glucose and neurotransmitters. There are also many reports where researchers have successfully demonstrated the detection of proteins, DNA, biomarkers, cells, microorganisms and other biomolecules.

4.1. Monosaccharides

4.1.1. Glucose

Glucose monitoring deserves a great deal of attention since diabetes management is of utmost concern for healthcare personnel, individuals and society as it is taking a heavy economic toll. About 285 and 439 million people will be affected by diabetes in 2010 and 2030, respectively (Shaw et al., 2009). The lifestyle and lifespan of the diabetics are mainly dependent on the accurate blood glucose monitoring, which helps in adjusting the dosage of insulin to be administered so that the glycemic values stays within the normal physiological range. About 85% of the biosensor market (~US\$ 8.5 billion) belongs to glucose sensors. Therefore, nearly all the sensing concepts are initially tested for the development of glucose sensors as it has a huge commercial impact. Most of the CNT-EC sensors have also been demonstrated for glucose monitoring applications (Table 1). Two types of CNT-EC sensing strategies, based on the presence and absence of enzyme as the biorecognition element, have been used for the detection of glucose.

4.1.1.1. Enzymatic. GOx, a flavin-dependent oxidase with specific activity for D-glucose, is easily immobilized on an Ag NP/CNT/CS composite (Lin et al., 2009a) for the sensitive detection of glucose with fast and steady responses. This strategy can also be employed for glucose sensing using MWCNTs and ZnO NPs (Wang et al., 2009b), where GOx is electrostatically bound to ZnO NPs due to the significant difference of the isoelectric point between GOx and ZnO NPs.

Table 4
Detection of other biomolecules.

Analyte detected	CNT modified electrode used	Detection range	Sensitivity	Reference
Fructose	D-fructose dehydrogenase (FDH) bound to MWCNTs synthesized on a Pt electrode	5–40 mM (LOD 5 mM)	N.M.*	Tominaga et al. (2009)
Galactose	Galactose oxidase (GalOD) covalently bound to chemically crosslinked SWCNTs-chitosan	Up to 1 mM (LOD 25 μ M)	1126 nA mM ⁻¹	Tkac et al. (2007)
<i>Aureococcus anophagefferens</i>	CNTs grown on 4 in. wafers and deposited with metal electrodes; functionalized with monoclonal antibody for <i>A. anophagefferens</i> ; Tween 20 used to counteract non-specific binding	10 ⁴ –10 ⁶ cells mL ⁻¹ (LOD 10 ⁴ cells mL ⁻¹)	N.M.*	Ishikawa et al. (2009)
MCF7 and BT474 human breast cancer cells	Single nanotube FET arrays functionalized with IGF1R-specific or Her2-specific antibodies	N.M.*	N.M.*	Shao et al. (2008)
K562/ADM and K562/B.W. cells	TiO ₂ /CNTs nanocomposite electrodes	N.M.*	N.M.*	Shen et al. (2008a)
<i>E. coli</i>	<i>E. coli</i> aptamer-functionalized SWCNT-FETs	N.M.*	N.M.*	So et al. (2008)
<i>Candida albicans</i>	Monoclonal anti- <i>Candida</i> antibodies adsorbed on SWCNTs FET, blocked with 0.5% Tween 20	(LOD 50 cfu mL ⁻¹)		Villamizar et al. (2009a)
<i>Salmonella infantis</i>	Anti- <i>Salmonella</i> antibodies adsorbed on SWCNTs FET, blocked with Tween 20	100–500 cfu mL ⁻¹ (LOD 100 cfu mL ⁻¹)	N.M.*	Villamizar et al. (2008)
DNA	Probe DNA immobilized on aligned MWCNT thin films; conjugating phosphatase after hybridization	50–200 nM (LOD 50 nM)	0.02 μ A nM ⁻¹	Berti et al. (2009)
Salmon sperm DNA	Probe DNA immobilized on aligned MWCNT thin films	0.5–10 μ M		Berti et al. (2009)
Target DNA sequences related to PAT gene in transgenic corn	Chitosan doped CNT film	0.5–20 nM (LOD 0.252 nM)	27.976 μ A M ⁻¹	Li et al. (2005)
PAT gene	GCE modified with MWCNT/nano ZnO/chitosan composite film	0.01 nM–1.0 μ M (LOD 2.8 $\times 10^{-12}$ M)	N.M.*	Zhang et al. (2008a)
	DNA-PDDA-PDC-SWCNT modified GCE	1.0 $\times 10^{-11}$ –1.0 $\times 10^{-6}$ M (LOD 2.6 pM)	–2.059 μ A M ⁻¹	Yang et al. (2008b)
PEPcase gene	PANF-MWCNT-CHIT-DNA modified CPE	0.1 pM–0.1 μ M (LOD 27 fM)	434.50 Ω M ⁻¹	Yang et al. (2009)
DNA	Ionic liquid supported CeO ₂ nanoshuttle-CNT composite	1 pM–0.1 μ M (LOD 0.23 pM)	5.285 Ω M ⁻¹	Zhang et al. (2009a)
	AgNPs/poly(3-(3-pyridyl) acrylic acid)/MWCNT composite; thiolated ss-DNA covalently linked to AgNPs	9.0 $\times 10^{-12}$ –9.0 $\times 10^{-9}$ M (LOD 3.2 $\times 10^{-12}$ M)	21.33 μ A M ⁻¹	Zhang et al. (2009d)
DNA hybridization	Nano Au-CNT/polyaniline nanofibers films	1.0 $\times 10^{-12}$ –1.0 $\times 10^{-6}$ M (LOD 5.6 $\times 10^{-13}$ M)	961.5 Ω M ⁻¹	Zhou et al. (2009)
DNA	SWCNT modified graphite electrodes			Yapasan et al. (2010)
Influenza virus (type A)	DNA covalently bound to amine-functionalized MWCNTs	1–10 nM (LOD 0.5 nM)	N.M.*	Tam et al. (2009)
Hepatitis C Virus RNA	Peptide nucleic acid adsorbed onto SWCNTs-FET	N.M.* (LOD 0.5 pM)	N.M.*	Dastagir et al. (2007)
HBV DNA	DNA oligonucleotides with thirteen guanine bases covalently bound to carboxylated MWCNTs on SPCE	5–40 μ g mL ⁻¹ (LOD 96 nM)	1.74 nmol L ⁻¹	Karadeniz et al. (2008)
	DNA oligonucleotides with thirteen guanine bases covalently bound to carboxylated MWCNTs on graphite electrode	N.M.* (LOD 184 nM)	N.M.*	Erdem et al. (2009)
HBV	Ag NPs-MWCNTs on GCE using Luteolin Copper (II) complex to detect hybridization	3.23 pM–5.31 nM (LOD 0.65 pM)	N.M.*	Niu et al. (2009)
Test DNA	Carboxy-MWCNTs covalently bound to 5'-amino end ssDNA	0.2–50 nM (LOD 0.1 nM)	42.73 μ A nM ⁻¹	Cai et al. (2003)
	PPy coated MWCNT-CPE	0.1–10 nM (LOD 85 pM)	N.M.*	Qi et al. (2007)
	DNA-NP zirconium oxide-MWCNT-chitosan modified GCE	0.149–93.2 nM (LOD 75 pM)	N.M.*	Yang et al. (2007)
	Layer-by-Layer MWCNT-PABA-AuNP modified GCE	1.0 pM–5.0 nM (LOD 0.35 pM)	N.M.*	Zhang et al. (2010b)
	ssDNA-pLys-SWCNT modified CPE	1 pM–0.1 μ M (LOD 0.31 pM)	N.M.*	Jiang et al. (2008)
	Carboxylic acid functionalized SWCNTs on GCE using ethyleneamine to fabricate an aligned electrode	40–110 nM (LOD 20 nM)	–0.0177 μ A nM ⁻¹	Zhang et al. (2009c)
	DNA-SWCNT-RTIL modified CPE	0.05–2.0 nM (LOD 9.9 pM)	N.M.*	Zhang et al. (2008a)
	Polymer coated CNT-FET electrodes with aminated-ssDNA	N.M.*	N.M.*	Martinez et al., 2009
	DNA-MWCNT modified GCE using rutin-Mn to detect hybridization	1.6–48 nM (LOD 38.1 pM)	N.M.*	Niu et al. (2008)
Adenine	β -Cyclodextrin/MWCNT modified electrode	4–20 μ M (LOD 0.75 $\pm$ 7.8% nM)	N.M.*	Shen and Wang (2009)
Guanine	β -Cyclodextrin/MWCNT modified electrode	100–280 μ M (LOD 33.67 $\pm$ 7.8% nM)	N.M.*	Shen and Wang (2009)
Thymine	β -Cyclodextrin/MWCNTs modified electrode	80–400 μ M (LOD 6.768 $\pm$ 7.8% nM)	N.M.*	Shen and Wang (2009)
Cholesterol	Cholesterol oxidase (ChOx) immobilized onto an IL-chitosan network modified MWCNT-Au NP composite	0.5–5 mM (LOD 0.5 mM)	200 μ A M ⁻¹	Gopalan et al. (2009)
	Cholesterol esterase (ChEt) and cholesterol oxidase (ChOx) immobilized on MWCNT/sol-gel-derived silica/chitosan nanocomposite	10–500 mg dL ⁻¹ (LOD 0.634 mg dL ⁻¹)	3.8 μ A mM ⁻¹	Solanki et al. (2009)
Choline	ChOx-IL-chitosan-Pt NPs-MWCNTs	4.79 μ M–0.3 mM (LOD 4.79 μ M)	0.044 A M ⁻¹ cm ⁻²	Tsai et al. (2008)
	Choline oxidase bound to MWCNT/polyaniline composite electrode	1 μ M–2 mM (LOD 0.3 μ M)	N.M.*	Qu et al. (2005)
Laccase	MWCNT modified electrode	1.37–33.79 UL ⁻¹ (LOD 1.37 UL ⁻¹)	0.473 μ A UL ⁻¹	
Lactate	Chitosan/polyvinylimidazole-Os/CNT/lactate oxidase network nanocomposite	5 μ M–1 mM (LOD 5 μ M)	19.7 μ A mM ⁻¹ cm ⁻²	Liu et al. (2008a)
	CNT/lactate oxidase/Si/ITO	10–50 mM	N.M.*	Cui et al., 2007
	Lactate dehydrogenase-Meldola's Blue-MWCNT paste electrode	0.1–10 mM (LOD 7.5 μ M)	3.46 μ A mM ⁻¹ cm ⁻²	Weber et al. (2006)
NADH	Lactate dehydrogenase-chitosan-MWCNTs on GCE	5–120 μ M (LOD 0.76 μ M)	0.0083 A M ⁻¹ cm ⁻²	Pereira et al. (2007)
	Sol-gel derived CNT ceramic composite electrode	12.4 μ M–0.65 mM (LOD 12.4 μ M)	2.31 μ A mM ⁻¹	Tsai et al. (2007a)
	Thionine cross-linked MWCNT/AuNP modified ITO electrode	0.5–237 μ M (LOD 0.1 μ M) (LOD 0.05 μ M with light irradiation)	17 nA μ M ⁻¹ 115 nA μ M ⁻¹ with light irradiation	Zhu et al. (2007)

Table 4 (continued)

Analyte detected	CNT modified electrode used	Detection range	Sensitivity	Reference
	Thionine incorporated CNT/Nafion-GCE	2–400 μM (LOD 1 μM)	4.7 mA M^{-1}	Huang et al. (2007)
	Varianine blue-SWCNT-COOH (treated with conjugation reagents DCC and NHS) modified screen-printed electrode	10 μM –50 mM (pH 5.0) (LOD 0.8 μM)	N.M.*	Radoi et al. (2008)
Estradiol	Poly(toluidine blue O)/MWCNTs/GCE	0.2 μM –4.5 mM (LOD 0.5 μM)	N.M.*	Zeng et al. (2006)
	Pt-MWCNT nanocomposite electrode	5.0×10^{-7} – 1.5×10^{-5} M (LOD 180 nM)	22.04 $\mu\text{A } \mu\text{M}^{-1}$	Lin and Li (2006)
Estrone	Pt-MWCNT nanocomposite electrode	2.0×10^{-6} – 5.0×10^{-5} M (LOD 840 nM)	N.M.*	Lin and Li (2006)
Estriol	Pt-MWCNT nanocomposite electrode	1.0×10^{-6} – 7.5×10^{-5} M (LOD 620 nM)	N.M.*	Lin and Li (2006)
HIV-1 PR	Thiol-terminated Fc-pepstatin self-assembled on Au electrode modified with thiolated SWCNT-AuNPs	0.8–1000 pM (LOD 0.8 pM)	N.M.*	Mahmoud et al. (2008)
HIV-1 PR inhibitors	Thiol terminated ferrocene (Fc)-pepstatin conjugate immobilized on a SWCNT/AuNPmodified Au electrode	0.8–80 pM (LOD 0.8 pM)	0.00247 mV pM^{-1}	Mahmoud et al. (2008a)
Folic acid	Ferrocenedicarboxylic acid-MWCNT paset electrode	4.6–152 μM (LOD 1.1 μM)	0.0115 $\pm$ 0.0006 $\mu\text{A } \mu\text{M}^{-1}$	Ensafi and Karimi-Maleh (2010)

*N.M.—Not Mentioned.

GOx and Pd NPs are co-deposited onto a Nafion-solubilized CNT film and used for glucose sensing (Lim et al., 2005). With increased storage stability and performance, the sensing approach displays no interferences from uric acid (UA) and ascorbic acid (AA). GOx is also adsorbed on an Au and Pt NPs modified self-assembled CNT electrode (Chu et al., 2007). A Nafion thin film is then covered on the GOx/Au NP/Pt NP/CNT electrode to prevent the enzyme loss and exclude any interference with AA and UA. In another approach, a plasma-polymerized film (PPF) based platform, where GOx and CNT film mixture is inserted with 10 nm-thick PPF, is used for glucose sensing (Muguruma et al., 2008).

An amperometric GOx electrode is fabricated using an EC active CNT dopant and the biocatalyst incorporated within an electropolymerized PPy film (Wang and Musameh, 2005). A glucose biosensor is also developed based on the incorporation of GOx into the colloidal Au-CNTs composite (Manso et al., 2007). The apparent Michaelis-Menten constant is 14.9 mM, implying high affinity of the enzyme towards the substrate under the microenvironment provided by AuNPs.

GOx bound ferrocene-modified MWCNT nanocomposites electrodes are prepared and employed for glucose sensing (Qiu et al., 2009) (Fig. 2). The enzymatic response to glucose oxidation is significantly improved as ferrocene serves as electron transfer mediator and MWCNTs acts as conductor. A glucose sensor is also demonstrated based on the binding of GOx to an O_2 plasma-functionalized MWCNT film on polydimethylsiloxane (PDMS) (Lee et al., 2009). The sensor is highly sensitive, possibly due to greater immobilization of enzyme, and/or higher electrocatalytic activity and electron transfer exhibited by the O_2 functionalized CNT film.

Boron-doped diamond (BDD) and CNT electrodes are used for glucose sensing by immobilizing GOx on a 3,3'-diaminobenzidine

(DAB)-electropolymerized electrode surface (Loh et al., 2004). CNTs modified with DAB show selective response to glucose at +0.3 V without any interference from AA and UA, whereas the DAB-modified BDD electrode without CNTs is not selective to glucose.

PtNPs (diameter 2–3 nm) and SWCNTs nanocomposites are used to develop a highly sensitive sensor for H_2O_2 (Hrapovic et al., 2004). SWCNTs are solubilized in Nafion and bind to PtNPs to fabricate nanocomposite electrodes. GOx is employed to fabricate a GC or carbon fiber microelectrode-based enzyme biosensor. The sensitivity for glucose detection is higher than GOx/GCE modified with PtNPs or CNTs alone.

Intensive studies on redox enzymes have advanced knowledge on electron transfer with electrodes in various ways. There is a great deal of interest in modifying electrode surfaces on the molecular scale with nanomaterials such as CNTs to promote direct electron transfer. The internal cavities and external sides of the CNT wall provide a platform for the accommodation of various biomolecules. This feature has inspired in coupling CNTs with glucose oxidase. However, the use of glucose oxidase encounters some interference from endogenous oxygen since it will interact with the reduced enzyme to form hydrogen peroxide, resulting in an underestimation of glucose unless oxygen is removed completely from the sample. It should be noted that biosensors for monitoring blood glucose use FAD- or NAD-dependent glucose dehydrogenase together with an artificial mediator since the measurement is no longer oxygen dependent. The incorporation of CNTs in such devices might impart the direct electron transfer between the enzyme and CNTs to avoid the use of the mediator. Some drug metabolites might react with the mediator and adversely affect the measurement. Glucose dehydrogenase (NAD dependent) is not very specific since it also catalyzes D-xylose, D-mannose, and D-maltose with a relative activity of 20%, 10% and 6%,

Table 5

Detection of pharmaceutical substances.

Analyte detected	CNT modified electrode used	Detection range (LOD)	Sensitivity	Reference
Salbutamol	CNT-Au layer	5–100 μM (LOD 1.0 μM)	0.0006 $\mu\text{A } \mu\text{M}^{-1}$	Karuwan et al. (2009)
Nimesulide	MWCNTs/GCE	0.32–65 μM (LOD 0.16 μM)	0.887 A M^{-1}	Zhang et al. (2010a)
Acetaminophen	Acid functionalized MWCNTs-GCE	3–300 μM (LOD 0.6 μM)	N.M.*	Allothman et al. (2010)
Rutin	MWCNT/ β -cyclodextrin film	40 μM –1 mM (LOD 20 μM)	0.5044 $\mu\text{A M}^{-1}$	He et al. (2006)
Clindamycin	MWCNT layer with a thin molecularly imprinted sol-gel film	0.5–80 μM (LOD 24.4 nM)	0.0429 $\mu\text{A } \mu\text{M}^{-1}$	Zhang et al. (2010c)
6-thioguanine	Thionine cross-linked MWCNT/AuNP modified ITO electrode	0.01–0.9 μM	1.7239 ± 0.0031 $\mu\text{A } \mu\text{M}^{-1}$	Ensafi and Karimi-Maleh (2010)
		0.9–100.0 μM (LOD 0.0085 μM)	0.0224 ± 0.0011 $\mu\text{A } \mu\text{M}^{-1}$	
Nicotine	MWCNT-alumina-coated silica/GCE	LOD 1.42 μM	1.786 A M cm^{-2}	Wang et al. (2009a)
8-azaguanine	MWCNT-dicetyl phosphate (DCP) film coated on a GCE	25 nM–10 μM (LOD 10 nM)	N.M.*	Lü (2004)

*N.M.—Not Mentioned.

Fig. 1. Schematic representation of the fabrication of ss-DNA/AgNPs/PPAA/MWCNTs-COOH on GCE and the hybridization detection of probe DNA by the modified GCE (Zhang et al., 2009d). Reprinted with permission from Elsevier Inc.

respectively compared to glucose. GOx is very specific, however, oxygen is a major concern and the result is dependent on the sample dissolved oxygen. However, a novel FAD-dependent glucose dehydrogenase was reported and this enzyme is very specific to glucose and uses a ferricyanide mediator (Tsujiyama et al., 2006). This enzyme is currently used by Abbott (Heller and Feldman, 2010) and Bayer (Toghiani and Compton, 2010) for *in vivo* glucose sensing with linearity ranging from 1 to 30 mM.

4.1.1.2. Non-enzymatic. A low-cost enzymeless glucose sensor can be made based on the directed and confined growth of CuNPs in self-assembled CNT films (Li et al., 2009a). A microbial biosensor for glucose is also developed based on the immobilization of *Pseudomonas putida* DSM 50026 cells on the CNT modified carbon paste electrodes using an Os-redox polymer (Timur et al., 2007). The Os-redox polymer effectively transfers electrons between the intracellular bacterial space and the electrode active area. Another glucose sensor is reported based on the ultrasonically-electrodeposited bimetallic PtM (M–Ru, Pd and Au) NPs on a CNT-IL composite film (Xiao et al., 2009). PtRu (1:1)-MWCNT-IL/GCE exhibits a higher active surface area with smaller electron transfer resistance among the various PtM-CNT composites. AA, UA, acetaminophen or fructose provokes no interference to the glucose detection.

Fig. 2. Amperometric responses of GOx/MWCNT-Fc/CS/GCE at an applied potential of +350 mV to successive addition of glucose in a stirred 0.1 M PBS. Inset: calibration curve (Qiu et al., 2009). Reprinted with permission from Elsevier Inc.

A simple strategy has been reported for fabricating a thin-film filtering membrane electrode (FME) of SWCNTs by vacuum filtration (Hu et al., 2010). The SWCNT-FME is applicable in two detection modes. The face-mode SWCNT-FME uses the exposed SWCNT sensing layer and functions as a thin-film EC sensor, whereas the back-mode SWCNT-FME has regulable listen selectivity. Furthermore, low-density discrete flower-like AuNPs or continuous AuNP films are electrodeposited on SWCNT-FME. The resulting SWCNT-AuNP composites show excellent electrocatalytic activity for glucose oxidation. Two oxidation peaks appear due to the direct electrochemical oxidation of glucose to gluconolactone at -0.30 V, followed by the oxidation of gluconolactone at $+0.21$ V. EC detection of glucose using CuNPs and CNTs is also described (Male et al., 2004). The SWCNT/CuNP composite electrode exhibits negligible responses to acetaminophen, AA and UA.

The detection of glucose at alkaline pH is not applicable for blood glucose monitoring without the sample pH adjustment and the detection is not specific for glucose (Male et al., 2004). It is appealing for the detection at physiological pH using nanocomposites of CNTs, however, substantial efforts must be devoted in this endeavor to encounter several technical challenges. Besides unproven selectivity for glucose, non-specific absorption/adsorption of chemicals of the blood and unknown drug metabolites with CNTs is highly anticipated, which might impede the use of this approach in blood glucose monitoring. A clear understanding of the mechanism of direct glucose oxidation needs to be established to pave the way for the design and development of non-enzymatic glucose sensing to meet all the requirements of blood glucose sensing with respect to selectivity, reproducibility, and reliability.

4.1.2. Fructose and galactose

D-fructose sensor is simply prepared by immobilizing D-fructose dehydrogenase onto a MWCNT modified Pt electrode (Tominaga et al., 2009). The apparent Michaelis-Menten constant of the immobilized enzyme is 11 ± 1 mM, illustrating its high affinity towards the substrate. Galactose sensing can be realized by covalent immobilization of galactose oxidase on chemically crosslinked SWCNT-chitosan (Tkac et al., 2007).

4.2. Neurotransmitters/Neurochemicals

Significant developments have taken place in the field of CNT based EC sensors for the detection of neurotransmitters/neurochemicals (Table 2). For instance, a sensitive thin-film transistor (TFT)

based ACh sensor is fabricated by depositing SiO₂ NPs on the self-assembled SWCNTs (Xue and Cui, 2008). Acetylcholine esterase (AChE) is then immobilized on the electrode and used as a sensing layer.

Epinephrine (EP) and norepinephrine (NEP) are difficult to distinguish using common EC methods owing to their structural and chemical similarity. Nevertheless, it is feasible to fabricate a selective sensor for EP using a CNT paste electrode modified with 2-(4-oxo-3-phenyl-3,4-dihydro-quinazolinyl)-N'-phenyl-hydrazinecarbothioamide (Beitollahi et al., 2008b). EP and NEP can be detected simultaneously by displaying two well-distinguished anodic peaks with a potential difference of 0.240 V. A CNT paste electrode modified with 2,2'-(1,2-ethanediybis(nitriloethylidene))-bis(hydroquinone) can detect EP in the presence of UA and folic acid (Beitollahi et al., 2008a). MWCNT modified GCE can also be functionalized with poly(methylene blue) (PMB) for detection of EP (Yogeswaran and Chen, 2008). The sensitivity and performance of the sensor are improved by the presence of PMB in the composite film. A SWCNT modified stainless steel microelectrode for EP sensing is designed based on an EC deposition technique (Valentini et al., 2007a). Another sensor for EP and NEP is based on a MWCNT-poly(nordihydroguaiaretic acid)-CS copolymer film on a screen-printed carbon electrode (Li et al., 2009a).

A nanohybrid modified electrode composed of MWCNT-silica network-AuNPs can detect AA in the presence of dopamine (Ragupathy et al., 2010). An AA sensor can be made using a film of overoxidized polypyrrole (PPy_{ox}) and SWCNTs to coat the surface of GCE (Li et al., 2007). The PPy_{ox}/SWCNT composite film detects AA in the presence of DA and UA. A paste electrode based AA biosensor comprising MWCNTs, Nafion and cobalt(II)-5-nitrosalophen (CoNSal) has also been reported (Shahrokhian and Zare-Mehrjardi, 2007a). The ΔE_p (potential separation between anodic and cathodic peak) for AA and UA at this sensor is ~315 mV.

The detection of DA by common EC sensors is difficult due to severe electroactive interference from elevated levels of AA in biological samples. However, a selective DA sensor can be prepared by covalent binding of SWCNTs to the interior of a conical glass micropore electrode (Cao et al., 2010). Nafion is employed to prevent the interference from AA. The selectivity issue can also be addressed by the immobilization of tyrosinase on a SWCNTs-PPy composite, since the enzyme only oxidize DA whereas AA remains uncatalyzed (Min and Yoo, 2009). Sodium dodecyl sulfate functionalized aligned MWCNT electrodes can be also used for DA detection (Zheng et al., 2008).

MWCNTs polymerized with a layer of molecularly imprinted polymer (MIP) poly-methacrylic acid (PMAA) have been attempted for detection of uric acid (Chen et al., 2010). Of interest is the development of a 2,2'-(1,2-ethanediybis(nitriloethylidene))-bis(hydroquinone) modified CNT paste electrode, which simultaneously detects UA and DA (Mazloun-Ardakani et al., 2009). An alternative strategy uses layer-by-layer (LBL) to form multilayer films consisting of SWCNTs and cetylpyridinium bromide (Zhang et al., 2007). The sensor simultaneously detects UA and DA in the presence of elevated AA concentrations. MWCNT-polylysine (Plys) modified GCE can also be used for sensing UA (Rodríguez et al., 2008) as it decreases the overvoltages for AA oxidation (440 mV), which effects the distinction of the oxidation of AA and UA.

A MWCNT-IL composite is capable of simultaneous detection of serotonin and DA (Sun et al., 2009). AA and other endogenous substrates such as glucose, NaCl, UA, purine, L-histidine and L-cysteine do not provoke any signal response. A SWCNT coated carbon fiber microelectrode exhibits high signal-to-noise ratio for *in vivo* detection of serotonin by fast scan voltammetry (Swamy and Venton, 2007). The microelectrode shows greatly reduced fouling compared to the bare electrode during the course of measurement.

A functional SWCNT film electrode is constructed on the surface of an inlaying ultra-thin carbon paste electrode (IUTCPE), where carbon paste is inlaid onto nichrome to form a precursor film (Wang et al., 2008). SWCNT/IUTCPE exhibits excellent electrocatalysis toward

xanthine, hypoxanthine and with distinct oxidation peaks. A highly sensitive, stable and rapid amperometric Xa biosensor can be prepared by immobilizing xanthine oxidase (XOD) on a silica sol-gel thin film-MWCNT modified GCE (Gao et al., 2009). Immobilized XOD retains its original activity towards Xa even after being entrapped in the composite film. The XOD-coated electrode shows long-term storage stability with a loss of only 5% activity after 90 days.

4.3. Proteins

4.3.1. Amino acids

A MWCNT-Cu₂O paste electrode can detect 19 amino acids (Dong et al., 2008). Combined capillary electrophoresis with amperometric detection is used for the detection of various amino acids such as arginine, tryptophan, histidine, threonine, serine, and tyrosine, which had high oxidation current responses. The analytical parameters are listed in Table 3. A rapid glutamate biosensor based on the oxidation of nicotinamide adenine dinucleotide (NADH) is prepared by immobilizing glutamate dehydrogenase (GLDH) on the SWCNT-thionine mediator (Meng et al., 2009a). The biosensor displays a wide linear detection range with high sensitivity (Fig. 3). Common interfering species such as AA, UA and 4-acetamidophenol do not interfere due to the low operating potential (+190 mV) vs. normal hydrogen electrode (NHE). An amperometric biosensor for glutamate can be prepared based on the self-assembly of GLDH and poly(amidoamine) dendrimer-encapsulated Pt NPs (Pt-PAMAM) onto MWCNTs (Tang et al., 2007). The GLDH/Pt-PAMAM_n/CNT modified electrode poised at 0.2 V detects glutamate in less than 3 s with high sensitivity and stability. In another strategy, MWCNTs, CS, Meldola's Blue (MDB) and GLDH based nanobiocomposite are used for the amperometric detection of glutamate (Chakraborty and Raj, 2007). Glutamate is determined from the enzymatically generated NADH and detected at -0.1 V with high sensitivity and without any interference from AA and UA. Besides sensing applications, the use of CNTs as catalyst support to construct functionalized nanocomposite interface for oxidation of NADH suggests great potential applications for the design of biofuel cells and bioelectronics.

Pt is deposited electrochemically on a CNT modified graphite electrode for detection of L-cysteine (Fei et al., 2005). A Nafion-CNT

Fig. 3. Successive amperometric responses of the GIDH-Thi-SWCNTs/GCE (a) and GIDH-SWCNTs/GCE (b) to the glutamate in PBS (0.1 M, pH 8.3) at +190 mV. Each addition of glutamate resulted in 50 μ M. The inset shows the dependence of the response of the GIDH-Thi-SWCNTs/GCE (a') and GIDH-SWCNTs/GCE (b') on glutamate concentration under the optimal condition (Meng et al., 2009b). Reprinted with permission from Elsevier B.V.

modified GC electrode is also described for the detection of homocysteine (Gong et al., 2004). The sensor shows better analytical properties in terms of stability, reproducibility and strong resistance against electrode fouling.

4.3.2. Immunoglobulin, albumin, and streptavidin

Fast and selective sensing of human IgG sensing is feasible by adsorption of human IgG on a SWCNT network field effect transistor (Cid et al., 2008). Tween 20 is used to block non-specific binding sites on SWCNTs to circumvent interferences resulting from the non-specific binding of proteins. An array of CNT electrodes can be used to develop a label-free immunosensor (Yun et al., 2007). The CNT electrodes are electrochemically activated and functionalized with carboxyl groups, followed by the covalent binding of anti-mouse IgG. The binding of mouse IgG molecules to the electrode is analyzed by cyclic voltammetry and electrochemical impedance spectroscopy.

The self-assembly of oxidative SWCNTs on Au has been attempted for detection of bovine serum albumin, BSA (Chen and Huang, 2009). An alternative strategy for BSA detection is the use of an avidin-MWCNT modified electrode, where biotinylated BSA tagged with tris (2,2'-bipyridine) ruthenium(II) label is bound to avidin. The electrochemiluminescence (ECL) response is generated in the tri-*n*-propylamine solution (Fang et al., 2008).

A label-free streptavidin biosensor uses SWCNT-FET fabricated by the self-assembly method (Hu et al., 2008). SWCNT-FET is also coated with polyethyleneimine or poly(ethylene glycol) (PEG) to reduce non-specific binding. The polymer-coated electrode is biotinylated and used for sensing streptavidin. Another streptavidin sensor is based on a supported lipid bilayer-SWCNT transistor (Zhou et al., 2007). Only lipid molecules are able to diffuse across SWCNTs since SWCNT acted as a barrier. The larger the CNTs, the greater is the size of the barrier thus leading to decreased diffusion. Therefore, the binding of streptavidin to the lipid bilayer could be detected using the SWCNT transistor as a charge sensor.

4.3.3. Insulin, human chorionic gonadotrophin and C-reactive protein

Ruthenium oxide (RuOx) can be electrodeposited onto a CNT layer and used as an insulin sensor (Wang et al., 2007). The sensor retains 97% activity after 60 min stirring of 2 μ M insulin solution. Of also interest is the development of a nanocomposite electrode composed of CNTs, CS and cobalt hexacyanoferrate NPs for detecting bovine insulin (Qu et al., 2006).

Toluidine blue (TB) and hemoglobin (Hb) can be incorporated on a MWCNT-CS modified GCE, followed by the deposition of an AuNP film by electrostatic adsorption and the attachment of anti-hCG for selective detection of human chorionic gonadotrophin (Li et al., 2008).

As an indicator of inflammation or acute infection, C-reactive protein (CRP) is associated with many diseases such as rheumatoid arthritis and cardiovascular disease. Of interest is the development of protein A-MWCNT modified screen-printed electrodes. Anti-CRP antibodies then bind in an oriented fashion by binding to protein A. This simple and inexpensive approach can detect CRP as low as 0.5 ng/mL (Buch and Rishpon, 2008), significantly below the clinically relevant threshold.

4.3.4. Cancer biomarkers

A CNT-FET based procedure involving the use of various linker-to-spacer ratios can be used for real-time detection of the prostate-specific antigen- α_1 -antichymotrypsin (PSA-ACT) complex, a prostate cancer marker (Kim et al., 2009). CNT-FET modified with only linkers cannot detect the PSA-ACT complex <500 ng/mL. In contrast, CNT-FET biosensors modified with the linker-to-spacer (1:3) is capable of detecting 1.0 ng/mL of PSA-ACT due to the effective blocking of the surface to prevent non-specific interaction.

Highly precise and sensitive detection of carcinoembryonic antigen (CEA) in saliva and serum is feasible by using a MWCNT screen-printed

electrode and ferrocene liposomes (Viswanathan et al., 2009). Monoclonal anti-CEA is covalently bound to a polyethyleneimine (PEI) wrapped MWCNT screen-printed electrode. Anti-CEA tagged ferrocene carboxylic acid (anti-CEA-FCL) encapsulated liposomes is used for the immunoassay at the secondary stage after CEA detection. AFP is detected in human serum by binding an AFP antigen onto GCE modified by AuNPs and a CNT doped CS (AuNP/CNT/CS) film (Lin et al., 2009a). A competitive immunoassay can be performed using sample AFP, immobilized AFP and alkaline phosphatase (ALP)-labeled antibody. The change in the amperometric response of 1-naphthyl phosphate by bound ALP label is proportional to the AFP concentration.

A conductive multilayer composed of Nafion-coated MWCNTs, thionine (Thi) and AuNPs is prepared by a novel self-assembly strategy (Fig. 4) to form a reagentless immunosensor (Su et al., 2009). The self-assembly procedure involves the dropping of the Nafion-MWCNT composite on the electrode surface and the chemisorption of Thi on carboxylic MWCNTs and Nafion. Negative-charged AuNPs are attached onto the Thi film by electrostatic interaction with the amino group of Thi.

SWCNT forests and glutathione protected AuNPs (GSH-AuNPs) can be used to detect interleukin-6 (IL-6), a human cancer biomarker, by sandwich immunoassays using multiple (14–16) HRP labels conjugated to a secondary antibody (Munge et al., 2009). The non-specific binding of labels is prevented by the BSA blocking. The GSH-AuNP based sensor is more sensitive with higher linearity than the SWCNT forest based sensor.

Putrescine, a potential biomarker for various cancer diseases, can be detected with high sensitivity by binding putrescine oxidase (POx) to 3-aminopropyltriethoxysilane solubilized MWCNTs (Luong et al., 2005). PDDA or poly(diallyldimethylammonium) chloride is also used to disperse MWCNTs and a mediatorless putrescine biosensor is constructed employing POx-MWCNT-GCE (Rochette et al., 2005). Putrescine can be detected at negative potentials without any interference from endogenous AA and UA. Putrescine in the plasma of cancerous mice is detected very quickly without any previous purification.

4.4. Cells

Algae are detectable by employing CNTs grown on 4 in. wafers and deposited with metal clusters (Ishikawa et al., 2009). The biosensor exhibits enhanced sensitivity by 2000-folds after metal clusters deposition as CNT channels are activated by the formation of Schottky junctions between CNTs and metal-clusters. *Aureococcus anophagefferens* and *BT3* algae, related to brown tides, can also be detected in real-time by CNT-EC biosensors. *A. anophagefferens* antibody functionalized CNT biosensors detects 10^4 cells/mL and Tween 20 is used to suppress the non-specific binding of *BT3*. A single nanotube FET array functionalized with IGF1R-specific and Her2-specific antibodies is capable of specific detection of MCF7 and BT474 breast cancer cells in human blood (Shao et al., 2008). Conductivity decreases by 60% when these single nanotube FET arrays detect BT474 or MCF7 breast cancer cells. Modified electrodes can also be fabricated by preparing TiO₂/CNTs nanocomposites and doping them on a carbon paper (Shen et al., 2008). These nanocomposites enhance heterogeneous electron transfer kinetics, leading to a significant increase in the relative detection sensitivity. There are clearly distinguishable changes in the EC signal and the contact angle in the presence of target cells such as K562/ADM and K562/BW. However, the selectivity of the technique has not been evaluated thoroughly for non-cancerous cells.

4.5. Microorganisms

Arrays of *E. coli* aptamer-functionalized SWCNT-FETs and a most probable number (MPN) table to estimate the MPN of *E. coli* has been described (So et al., 2008). SWCNT-FETs are selective as shown by the decrease in conductance of more than 50% in the presence of *E. coli* whereas a high-density *Salmonella* sample provokes no signal response.

Fig. 4. (A) Schematic illustration of the stepwise immunosensor fabrication process. (B) Calibration plots of the changes of the peak current response vs. concentration of AFP with (a) anti-AFP/AuNPs/Thi/Nafion-MWCNTs/GCE, and (b) anti-AFP/AuNPs/Thi/Nafion/GCE. (Su et al., 2009). Reprinted with permission from Elsevier Ltd.

Similarly, *Candida albicans* can be detected by using monoclonal anti-*Candida* antibodies adsorbed onto SWCNT-FET (Villamizar et al., 2009a). The monoclonal antibodies enable the specific binding of fungal antigen without any interference with two competing yeasts: *Cryptococcus albidus* and *Saccharomyces cerevisiae*. The biosensor detects <50 cfu/mL in 1 h with stable responses for over 10 days. A similar procedure is used for the development of a highly selective FET biosensor for *Salmonella infantis* where the SWCNT network serves as the conductor channel. Anti-*Salmonella* antibodies adsorbed onto SWCNTs serve as a specific biorecognition element, and Tween 20 is capable of preventing the non-specific interactions (Villamizar et al., 2008). The biosensor detects <100 cfu/mL in 1 h and exhibits no binding at 500 cfu/mL of *Streptococcus pyogenes* and *Shigella sonnei*.

4.6. DNA

The EC method is a simple and cost-effective strategy for highly-sensitive and rapid detection of DNA hybridization (Table 4). Aligned CNT thin films can be employed for DNA sensing by binding probe DNA and detecting its hybridization with the target DNA (Berti et al., 2009). The enzyme-labeled method (involving conjugation of phosphatase after hybridization and detection of enzymatically produced *p*-amino phenol in *p*-amino phenyl phosphate buffer solution) for the detection of DNA is much more sensitive than the label-free method. A biosensor has been developed for detecting salmon sperm DNA using CS doped with CNTs (Li et al., 2005). CNTs enhance the electroactive surface area, leading to the increase in the electron transfer rate between methylene blue (MB) and the electrode. A GCE/MWCNT/nano ZnO/CS nanocomposite electrode was used for the detection of various target DNA sequences related to

the PAT gene in the transgenic corn (Zhang et al., 2008a). An AgNPs/poly(3-(3-pyridyl) acrylic acid)/MWCNTs nanocomposite electrode, where thiolated single-stranded probe DNA is bound covalently to AgNPs using a 5' thiol linker, has been used for detecting DNA hybridization (Zhang et al., 2009d). The response signal of intercalated Adriamycin, corresponding to the DNA hybridization, is detected by differential pulse voltammetry.

A highly sensitive technique based on impedance spectroscopy was reported for detecting DNA hybridization (Zhou et al., 2009). The detection sensitivity for the PAT gene sequence is greatly increased by using nano Au-CNT/polyaniline nanofibers films for binding probe DNA. A rapid, reproducible and sensitive method is also developed for the biomolecular recognition of cis-diamminedichloroplatinum, an anticancer drug using SWCNT modified disposable graphite electrodes. SWCNTs are capable of enhancing the guanine oxidation signal (Yapasan et al., 2010) of differential pulse voltammetry and EC impedance spectroscopy. Another anticancer agent oxaliplatin has also been tested.

The probe DNA is covalently bound to the amine-functionalized MWCNTs for detection of Influenza virus (type A) (Tam et al., 2009). The target DNA is detected by the change in the surface conductance of the sensor after hybridization with the probe DNA. The simultaneous determination of adenine (A), guanine (G) and thymine (T) in the analyte mixture using a β -CD/MWCNT modified electrode has also been reported (Shen and Wang, 2009). Well-separated voltammetric peaks are obtained between G and A (330 mV), and A and T (170 mV).

4.7. Other biomolecules

CNT-based EC sensors have been demonstrated for the detection of various other biomolecules (Table 5). A stable and specific cholesterol

sensor is indeed demonstrated by immobilizing cholesterol oxidase (ChOx) onto an IL-CS network modified MWCNT-AuNP composite (Gopalan et al., 2009). There is no interference from UA, AA and acetaminophen. Cholesterol esterase (ChEt) and ChOx can be co-immobilized onto the MWCNT/sol-gel-derived silica/CS nanocomposite for the determination of the total cholesterol (Solanki et al., 2009).

A MWCNT modified electrode using ferrocenedicarboxylic acid as a mediator is capable of detecting folic acid (Ensafi and Karimi-Maleh, 2010). This sensor exhibits efficient electrocatalytic activity towards the oxidation of folic acid at pH 9.0. Choline oxidase bound to a nanocomposite electrode, composed of functionalized CNTs and a PANI multilayer film, is employed for detection of choline (Qu et al., 2005).

A MWCNT modified electrode described by Liu et al. (2008a) is capable of detecting laccase's activities from *Penicillium simplicissimum* in the compost. CNTs greatly enhance the EC signal, resulting in rapid and higher sensitive responses compared to spectrophotometry. A chitosan/polyvinylimidazole-Os/CNT/lactate oxidase network nanocomposite is also used to develop lactate biosensor (Cui et al., 2007). A NADH sensor is developed using the sol-gel derived CNT ceramic composite electrode (Zhu et al., 2007). A highly sensitive estrogens sensor for detecting estradiol, estrone and estriol has been reported using a Pt nano-cluster/MWCNT modified electrode (Lin and Li, 2006). A Pt-MWCNT nanocomposite electrode exhibits higher sensitivity and catalytic activity than the MWCNT and PtNP modified electrode.

Ferrocene (Fc)-pepstatin-modified surfaces can be used for the picomolar detection of human immunodeficiency virus type-1 protease (HIV-1 PR) (Mahmoud et al., 2008). Thiol-terminated Fc-pepstatin is self-assembled on the surface of Au electrode modified with AuNPs or thiolated SWCNTs/AuNPs. SWCNTs/AuNPs electrode shows high detection sensitivity for HIV-1 PR. A similar procedure is followed for the highly sensitive screening assay to evaluate four potent HIV-1 PR inhibitors (lopinavir/ritonavir, saquinavir, indinavir and fosamprenavir) at picomolar levels (Fig. 5) using a thiol terminated Fc-pepstatin conjugate bound to SWCNTs/AuNP/Au electrode (Mahmoud and Luong, 2008). The same research group further described a rapid and simple electrochemical detection method to detect the presence of protease (HIV-1 PR) in HIV patients' sera. In this assay format, disposable screen printed gold electrode (SPGE) surface was modified with gold nanoparticles (AuNPs) or thiolated single-walled carbon nanotubes/gold nanoparticles (SWCNT/AuNPs). Thiol-terminated ferrocene (Fc)-pepstatin was then self-assembled on such modified surfaces. The interaction between the Fc-pepstatin modified substrates and HIV-1 PR was confirmed by scanning electron (SEM) and atomic force microscopy (AFM) and probed by differential pulse voltammetry (DPV). A linear relationship was observed between the shift in peak potential and the increasing number of HIV-1 viral replications in the HIV-infected serum samples (Mahmoud and Luong, 2010).

5. Pharmaceutical applications

Salbutamol can be detected using a CNT electrode and flow injection based microfluidic device (Karuwan et al., 2009). A MWCNTs modified GCE is also employed for the detection of nimesulide (Zhang et al., 2010a), resulting in an increase in sensitivity of about 7-folds in comparison to GCE. The reduction peak potential of nimesulide shifts positively from -0.665 V at a bare GCE to -0.553 V at a MWCNTs/GCE. The GC electrode modified with acid treated MWCNT is employed to simultaneously detect acetaminophen (AP) and DA (Alothman et al., 2010) without any interference from AA, UA and NADH (Table 6).

A MWCNT/ β -CD film can detect rutin based on the preconcentration effect of β -CD for rutin (He et al., 2006). The biosensor shows much better analytical performance than the MWCNT film or the bare

GCE alone. Clindamycin is selectively detected using a MWCNT layer with a thin molecularly imprinted sol-gel film formed by electrochemical deposition (Zhang et al., 2010c). 6-Thioguanine (6-TG) is detected employing a MWCNT modified electrode using ferrocenedicarboxylic acid as a mediator (Ensafi and Karimi-Maleh, 2010). The sensor exhibits efficient electrocatalytic activity towards the oxidation of 6-TG at pH 9.0. A MWCNTs-alumina-coated silica (ACS) nanocomposite modified GCE is used for detecting nicotine (Wang et al., 2009a). The MWCNT-ACS nanocomposite requires lower electro-oxidation potential, thus preventing the electrode fouling apart from increasing the current response. 8-azaguanine can be selectively detected in human urine using a MWCNT-DCP film coated GCE without any interference from various metallic cations and organic compounds Lü (2004).

6. Technical challenges and future directions

CNTs have been proven as promising materials for the development of advanced biosensors with improved detection sensitivity and selectivity. CNT-based electrodes can be poised at low potentials for NADH and H_2O_2 , two important by-products of over 800 important enzymes. CNTs might also act as nanowires to promote or impart the direct electron transfer with various oxidases such as glucose oxidase and putrescine oxidase to simplify the design and implementation of the detection scheme. Therefore, CNTs have been advocated as molecular probes, with numerous potential applications in biosensing. Besides liquid phase applications, the electrical resistivities of SWCNTs change sensitively on exposure to NO_2 , NH_3 and O_2 with very fast response times compared to metal-oxide and polymer based sensors. This feature might offer an opportunity for the development of gas phase sensors using CNTs. Of also interest is the organization of the protein molecules on CNTs which corresponds to the helicity of the nanotubes. Thus, CNTs with controlled helicities could be recognized by organic molecules of comparable length scales. However, the selection of the size and helicity of CNTs during growth remains a formidable task.

The immobilization of biomolecules on the carbon nanotube structure without affecting their bioactivity is the prerequisite. To date, nanotubes with the attachment of acidic functionalities have been common and simple; the use of metallic nanoparticles, particularly gold nanoparticles has emerged since biomolecules can be engineered to self-assemble on the CNT-gold nanocomposite. Owing to their very small pore sizes, the filling of nanotubes with biomolecules is very difficult if not impossible as the filling can only be attained for a selected few compounds. For electrochemical biosensing, randomly entangled carbon nanotubes have been physically coated onto conventional electrodes. The use of vertically aligned carbon nanotubes, coupled with well-defined chemical functionalization, might offer better sensitivity and good selectivity. However, the progress in this area is still very limited, owing partly due to its high production cost for large scale applications. However, it is not really possible yet to grow these structures in a controlled way and the growth mechanism of nanotubes, similar to fullerenes, has remained a mystery. Some successes in growing CNTs of certain diameters are simply achieved by trial and error. In this context, graphene could be a formidable competitor of CNTs since the former also exhibits several unique characteristics, including being easy and relatively inexpensive to make.

The use of CNTs for testing with "real world" samples might be problematical since several endogenous species in such samples are anticipated to display hydrophobic interactions with CNTs. Electroactive interference is always of great concern due to moderately high anodic potentials, leading to the overestimation of the target analyte level. As an example, the amperometric detection of blood glucose is interfered by endogenous electroactive compounds such as uric acid, ascorbic acid, dopamine, and L-cysteine. The presence of drug and

Fig. 5. Schematic illustration for the preparation of Fc-pepstatin conjugate/thiolated SWCNT and AuNP modified electrodes and their use for detecting HIV-1 protease and the subsequent assay of HIV-1 protease inhibitors (Mahmoud and Luong, 2008). Reprinted with permission from American Chemical Society.

drug metabolites is another issue which requires careful investigation since they are often electroactive as exemplified by acetaminophen and salicylic acid, a component of aspirin. New drugs and chemicals are always being produced by the pharmaceutical industry, therefore, their potential impact on the selectivity and sensitivity of CNT-sensors/biosensors need to be considered. Tolazamide, a sulfonamide drug for the control of blood glucose levels, causes significant interference during glucose sensing. Sensitive and selective sensing is not only relevant in clinical chemistry but also in food quality and control, environmental chemistry and bioprocessing. Thus, the design and development of CNT-based sensing schemes require a renewed approach to circumvent such electroactive and pharmaceutical interferences.

Recently, metal oxides have been used together with CNTs for the fabrication of different sensors/biosensors. Although unmodified CNTs are resistant to surface fouling and virtually unaffected by chloride, the modification of CNTs with popular Pt nanoparticles need to be addressed thoroughly. Besides chloride anions which strongly chemisorb to the surface of platinum, amino acids and proteins are known to adhere strongly to the surface to render the surface inaccessible to the target analyte, i.e., severe electrode fouling. Indeed, non-specific binding of proteins on CNTs is commonly found with a wide range of proteins. Of interest to note that CNTs modified with MnO_2 exhibits high tolerance to electrode fouling with no interference from chloride.

Fullerenes failed to make much of an impact in applications and it is hopeful that the story of nanotubes will be very different since various countries have invested heavily in developing nanotube applications. Commercially purified CNTs are only 80–95% pure which could be an additional disadvantage for some bioapplications, e.g., implantable devices where the purity of 99% or even higher is mandatory. Moreover, extensive cytotoxicity analysis of such devices

needs to be done. Cytotoxicity of CNTs appears to depend on a number of factors such as the material preparation, impurities, geometry and surface functionalization. Most of the reported literature till date shows the highly contradictory cytotoxicity analysis of CNTs (Cui et al., 2010), which stress the need for standard international guidelines for cytotoxicity determination. There are currently very few standards for carbon nanotubes and there is no life cycle assessment or risk assessment for CNTs. Without the standards for CNTs, it will be difficult to compare CNTs from different suppliers whereas risk assessment and life cycle assessment will influence the design, development, manufacturing and marketing of CNT-based devices. Micro/nanofabrication technology has been devoted to fabricate CNT arrays, biologically and chemically functionalized CNTs, and sensors based on conjugated polymers. These CNT-EC sensors can selectively detect very low concentration of analytes. Improved micro/nanofabrication technology will be developed for integrating nanosensors into functional devices, which will incorporate microfluidics for the parallel real-time monitoring of multiple analytes. The key question remains as how to make them cheaply, reproducibly and predictably and this issue is just beginning to be addressed.

More economical ways to grow CNTs as well as to connect them to electrical contacts must be developed. The utilization of electric forces to grow carbon is not cost-effective and cannot be used for mass production. NanoIntegris Inc., USA has developed a proprietary technology to develop electronically pure (up to 99% pure) metallic and semiconducting SWCNTs. However, still more research efforts are required to arrive at highly pure CNTs having greater than 99.99% purity as even the minute amounts of impurities may impact their behavior. Therefore, based on the challenges in the technology, CNT-EC sensing technology is not ripe enough to make realistic commercial products as it cannot fulfill the desired quality control standards

Table 6
Purity of commercially available CNTs.

S.No.	CNTs	Purity	Company	Website
1	Metallic, semiconducting & ultra-high purity SWCNTs	99%	NanoIntegris Inc., USA	www.nanointegris.com
2	MWCNT; SWCNT; CNT-COOH; CNT-Amide	>95%	NanoLab, Inc., USA	www.nano-lab.com
3	CNTRENE [®] CNT solutions	N.M.*	Brewer Science, USA	www.brewerscience.com
4	As-produced, Pre-purified & Purified SWCNT	97%	Nano-C, USA	www.nano-c.com
5	SWCNT; MWCNT	N.M.*	Thomas Swan, UK	www.thomas-swan.co.uk
6	SWCNT; MWCNT; DWCNT	90–95%	Helix Material Solutions, USA	www.helixmaterial.com
7	SWCNT; MWCNT; DWCNT; Conducting (Metallic) & Semiconducting SWCNT; -OH & -COOH functionalized SWCNT & MWCNT	N.M.*	Mknano, Canada	www.mknano.com
8	SWCNT; DWCNT; aligned MWCNT; regular- & short-length MWCNT; -OH & -COOH functionalized, dispersible CNTs; special CNTs	95%	Nanostructured & Amorphous Materials, Inc., USA	www.nanoamor.com
9	SWCNT; MWCNT; -OH & -COOH functionalized SWCNT & MWCNT	90–95%	SkySpring Nanomaterials, Inc., USA	www.ssnano.com
10	SWCNT; DWCNT; MWCNT; -OH & -COOH functionalized SWCNT, DWCNT & MWCNT	80–90%	Arry International GmbH, Germany	www.arry-nano.com
11	SWCNT; MWCNT; functionalized CNTs (custom made)	90–98%	SouthWest NanoTechnologies Inc., USA	www.swentnano.com
12	MWCNT; Field emission grade CNTs; vertically aligned MWCNT on substrates	80–90%	Xintek Inc., USA	www.xintek.com
13	CNT (custom made)	>93%	Nanocarbon Sales, Canada	www.nanocarbonsales.com
14	SWCNT; MWCNT; -OH & -COOH functionalized SWCNT & MWCNT	80–90%	Nanos shel, USA	www.nanoshel.com
15	SWCNTs (as prepared; purified, low functionality; purified high functionality; amide functionalized; organic soluble; water soluble)	>80%	Carbon Solutions, Inc., USA	www.carbonsolution.com
16	SWCNT; DWCNT; MWCNT	>90–95%	SES Research, USA	www.sesres.com
17	SWCNT; DWCNT; MWCNT; -OH & -COOH functionalized CNTs	>90–95%	Cheap Tubes Inc., USA	www.cheaptubes.com
18	SWCNT; DWCNT; MWCNT; -OH & -COOH functionalized CNTs; aligned MWCNTs	90–95%	Sun Innovations, Inc., USA	www.nanomaterialstore.com
19	MWCNT	>93%	Fibermax Composites, Greece	www.fibermax.eu
20	SWCNT; MWCNT; -OH, -NH ₂ & -COOH functionalized CNTs; graphitized MWCNTs; short MWCNTs	>90–97%	Feibo (ShangHai)Chemical Technology Co., Ltd., China	www.arknano.com
21	SWCNT; DWCNT; MWCNT; -OH, -NH ₂ & -COOH functionalized CNTs; graphitized MWCNTs; Ni-coated MWCNTs; aligned CNTs; helical CNTs	>90–95%	Times Nano, China	www.timesnano.com

*N.M.—Not Mentioned.

posed by Food and Drug Administration (FDA) and other certification agencies.

There have been continuously increasing reports for the development of CNT based EC sensors in the past decade and most of the researchers and companies are progressing towards the protection of their intellectual property in this area as shown by the increasing number of patent applications filed. As the field of CNT based EC sensors is evolving and maturing very rapidly, it is most likely that the existing challenges in the commercialization of these sensors would be effectively tackled by the technology developments in near future. The continuous development in this area would further lead to cost-effective and reproducible manufacturing techniques; methods for electrode improvement; miniaturized prototypes with lesser power consumption; and, robust, reproducible and highly sensitive sensors. Last but not least, the current market price of CNTs is also too high presently for any realistic commercial application. In the last few years, there have been several companies that were set up in many different countries, particularly the USA and China, to produce and market nanotubes. It remains to be seen whether CNTs will be available to consumers for less than US \$100/kg. Currently, single walled CNTs with over 90% purity are marketed for almost US \$40,000/kg compared to \$US 2000–3000/kg for multi-walled CNTs with purity over 95% (<http://www.cheaptubesinc.com/carbon-nanotubes-prices.htm>).

The use of fragile biorecognition molecules such as enzymes, proteins, etc. in biosensors has limited their widespread applications. Robust molecular imprinting polymers can be used in the development of sensors capable of recognizing certain organic compounds, but selectivity is still problematic and less applicable for recognizing

macromolecules such as proteins and polypeptides. Non-enzymatic sensors using CNTs and/or other nanomaterials have raised particular interest and non-enzymatic glucose sensing by unmodified CNTs has become feasible (Ye et al., 2004) and different metal oxides can be used together with CNTs to fabricate electrocatalytic glucose sensors (Toghiani and Compton, 2010). However, linearity is very limited; rarely exceed 15 mM compared to 30 mM for enzyme-based glucose sensors. Non-enzymatic sensing might offer cost effectiveness, long-term stability, and thermal tolerance. However, the mechanism for direct glucose oxidation, a prerequisite for the design and development of non-enzymatic glucose sensors remains unsolved and to date, this approach has not fulfilled the entire requirement for selective detection of blood glucose. A lack of selectivity for glucose is the key issue in addition to frequent electrode fouling and the detection does not fare well at physiological pH. Also of importance is to design a blood glucose monitor that requires only 0.3 µL or less of medium for glucose detection. In this context, electrochemical sensing outperforms photometric, light absorption, and reflection-based home blood glucose monitors which require a volume of 3–10 µL.

The chapter cannot be concluded without a slight cautionary note. CNTs might not be an answer for all applications in biosensing and nanobiotechnology. Other carbon-based nanomaterials such as doped diamond like-materials and graphene have emerged and also opened new avenues toward the development of new and/or improved electrochemical biosensing schemes. Despite biosensors have been developed for numerous analytes, glucose biosensors are still a highly active area of biosensor research and account for over 80% of the biosensor industry. Besides glucose, recent electrochemical research has

focused on the detection of neurotransmitters such as dopamine and its derivatives. Of further interest is the detection of glycated hemoglobin, a biomarker used to follow long-term blood glucose level (Park et al., 2008).

Disposable “fingerstick” glucose biosensors involve mass production of a mixture of enzymes, mediators and stabilizers on a carbon sensing substrate. It remains to be seen whether CNTs can play any significant role in the fabrication of such devices. Many pending issues such as processing, mass production and the time frame required to launch new products to market still have to be resolved and whether CNTs result in disruptive technologies. Nevertheless, commercial carbon-nanotube gas sensors are already on the market. Nanomix offers a sensor with a special recognition layer for selective hydrogen binding over common interferants such as ammonia, methane, carbon monoxide, carbon dioxide, and hydrogen sulfide (<http://www.azonano.com/news.asp?newsID=914>).

The design and fabrication of electrochemical biosensors using CNTs together with nanoscale materials remains a vibrant research area. Glucose sensing will be still the most important research area considering over 10 billion glucose assays need to be performed by diabetic people. However, for commercial viability CNT-based sensors must be manufactured with high consistency and cost-effectiveness so that they can compete with other commercially available products. It is a formidable task to translate research findings into product lines and doubtlessly some endeavors will succeed while some will fail miserably. One of the main reasons is the exorbitant cost of introducing a new device to compete with existing technologies. As an example, the cost of introducing a continuous glucose monitoring system is over US\$100 million, which is beyond the means of a small enterprise (Heller and Feldman, 2010).

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