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Enhanced Electrochemical Sensing with Carbon Nanotubes Modified with Bismuth and Magnetic Nanoparticles in a Lab-on-a-Chip

Dr. Preetha Jothimuthu^a, Dr. Joe L. Hsu^b, Dr. Robert Chen^c, Dr. Mohammed Inayathullah^a, Dr. Venkata Raveendra Pothineni^a, Antony Jan^d, Dr. Geoffrey C. Gurtner^e, Dr. Jayakumar Rajadas^a, and Dr. Mark R. Nicolls^b

Jayakumar Rajadas: jayraja@stanford.edu; Mark R. Nicolls: mnicolls@stanford.edu

^aBiomaterials and Advanced Drug Delivery Laboratory, Stanford University, Stanford, CA, 94305 (USA)

^bDepartment of Medicine, Division of Pulmonary & Critical Care Medicine, VA Palo Alto/Stanford University, Stanford, CA, 94305 (USA)

^cStanford Nanofabrication Facility, Stanford, CA, 94305 (USA)

^dDepartment of Electrical Engineering, Stanford University, Stanford, CA, 94305 (USA)

^eDepartment of Surgery, Stanford University School of Medicine, Stanford, CA, 94305 (USA)

Abstract

Iron plays an especially important role in human physiological functions and pathological impairments. The superior properties of carbon nanotubes (CNTs) and their modification with bismuth and magnetic nanoparticles as developed in this work have led to an extraordinary and novel material to facilitate ultrasensitive detection in the nanomolar range. Here, we present the development of an electrochemical sensor for detection of ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron by means of CNTs modified with bismuth and magnetic nanoparticles for higher sensitivity of detection. The sensor fabrication includes microfabrication methodologies, soft lithography, and electrodeposition. Cyclic voltammetry and differential pulse voltammetry are used for the electroanalytical studies and detection of the ions in samples. The sensor has a dynamic range of detection from 0.01 nM to 10 mM. The performance of the sensor with modified CNTs was explored for sensitivity and specificity. CNTs, modified with bismuth and magnetic nanoparticles by means of electrodeposition, enhanced the detection limit significantly down to 0.01 nM.

Keywords

carbon nanotubes; electrochemistry; lab-on-a-chip; sensors; voltammetry

Correspondence to: Jayakumar Rajadas, jayraja@stanford.edu; Mark R. Nicolls, mnicolls@stanford.edu.

Conflict of Interest

P.J., J.L.H., G.C.G., J.R. and M.R.N. are listed on the following provisional patent application assigned to Stanford University: [Enhanced Electrochemical Sensing With Carbon Nanotubes Modified With Bismuth And Magnetic Nanoparticles] (S16119).

Introduction

There is a large unmet medical need for the detection and quantification of iron in bodily fluids. Iron disorders in iron metabolism and relevant therapeutic measures have been and remain an important focus of study.^[1] Iron disorders can be divided into conditions of iron deficiency or iron overload.^[2] For example, the accumulation of iron in the synovial membrane and fluid of rheumatoid arthritis patients likely contributes to disease progression.^[3] Diseases of iron metabolism include bone loss in iron overloaded patients, liver damage attributed to iron overload, and iron deficiency anemia.^[4–6]

Among various other applications, electrochemical sensors are the primary technology used for the detection of metal ions. Currently, mercury-based electrodes, carbon-based electrodes (screen printed carbon and carbon paste), platinum electrodes, and bismuth electrodes are the conventional materials utilized in sensors. Miniaturization of these electrodes can be associated with rapid detection and smaller sample volumes relative to conventional atomic absorption spectroscopy (AAS) and inductively coupled plasma mass spectroscopy (ICPMS) methods of detection. There is significant potential for the development of a point-of-care diagnostic tool as well as bedside monitoring in hospitals in which small size, portability, and speed are highly desired device features.

Electrochemical electrodes have been used to detect Fe^{2+} and Fe^{3+} utilizing a glassy carbon electrode in a flow through cell configuration which required 2 mL min^{-1} of sample volume introduced into the reagent mixture and calibrated for 10^{-6} to 10^{-8} M .^[7] Alternatively, use of a hanging mercury drop electrode (HMDE) to detect iron in sea water samples in the range of $0.03\text{--}70 \text{ ng mL}^{-1}$ have been demonstrated using adsorptive cathodic stripping voltammetry.^[8] Previously, a flow injection method of determination of Fe^{2+} and Fe^{3+} utilized an opto-electrochemical flow through cell and a study of interfering ions such as Cu, Mn, Zn, Hg, Cr, Cd, Ni, Co, Mo, and Vo for the detection of Fe^{2+} and Fe^{3+} ions was reported.^[9] Alternatively, a modified glassy carbon electrode for selective detection of Fe^{3+} has been effective with a detection limit of $2\text{--}3 \text{ ppb}$.^[10]

Carbon nanotubes (CNTs) are highly promising because of their excellent biophysical properties including high electrical conductivity, mechanical strength, increased surface area with the porous surface, chemical stability and high electron transfer rate properties, which make them highly attractive for a number of applications and implementations. The electrochemical properties of CNTs have been investigated and reported by studies on the electrochemical behavior of CNT film electrodes in a 1 mM Fe^{2+} solution.^[11] Another process utilized electrostatic spray deposition (ESD) of CNT solution onto a metallic substrate and evaluated the electrochemical properties by means of cyclic voltammetry.^[12] Additional studies demonstrated modification of glassy carbon electrode with multiwalled CNTs and iron(III) porphyrin film for the detection of chlorate, bromate, and iodate and dopamine and serotonin, respectively.^[13, 14]

Bismuth as a working electrode is now being exploited because of its wide potential window of detection, comparable to mercury electrodes, and its nontoxic properties that make it advantageous for biosensing. A bismuth-based lab-on-chip sensor for the detection of Mn,

Zn, Pb, and Cd highlights the potential of using this metal as a sensor material.^[15, 16] Modifying CNTs with bismuth permitted the trace metal analysis of Zn, Cd, and Pb and compared the performance to glassy carbon, graphite, activated carbon, and bare CNTs. These investigators fabricated the electrodes by making a paste of the electrode material and screen printing them.^[17]

Magnetic nanoparticles such as iron oxide particles exhibit excellent electrochemical properties and have been coated on electrodes for the detection of ions. Iron oxide coated glassy carbon electrode has also been demonstrated for ultrasensitive detection of heavy metals including Zn^{II} , Cd^{II} , Cu^{II} , Hg^{II} , and Pb^{II} ions.^[18, 19] Other research attributed the electrochemical performance of Fe_2O_3 in the detection of Pb ion to be dependent on the facet of the Fe_2O_3 nanostructure, particularly the facets $\{012\}$, $\{001\}$, and $\{110\}$ of the nanocube, nanorod, and nanoplates structures.^[20] Further studies focused on synthesizing Fe_2O_3 with these effective facets exposed for the demonstration of detection of As^{III} .^[21]

Magnetic nanoparticles are being used to modify CNTs to concentrate and capture analytes.^[22–24] Carbon nanotubes modified with platinum–iron(III) nanoparticles on glassy carbon electrode for the detection of As^{III} were demonstrated by means of co-deposition of Pt and Fe^{III} on the CNTs dispersed in nafion composite.^[25] Carbon-coated iron nanoparticles have been used with direct electrochemistry of hemoglobin for amperometric detection of hydrogen peroxide.^[26] Other work on modified CNTs reported an amperometric glucose biosensor based on multiwalled CNTs with SiO_2 -coated Fe_3O_4 magnetic nanoparticles ($\text{Fe}_3\text{O}_4@ \text{SiO}_2/\text{MWNTs}$) and a glucose sensor based on Pt-nanoparticle-decorated iron oxide multiwall CNTs ($\text{Fe}_y\text{O}_x\text{-MWCNTs}$) magnetic composite.^[27–29] Detection of catechol using magnetic nanoparticles (Fe_3O_4) grafted onto multiwall CNTs has also been reported.^[29] Some of the reported work described that the addition of magnetic nanoparticles to the CNTs made the CNTs magnetized.^[30, 31] Another interesting application showed silver nanoparticles cross-stacked with CNTs to form sheets that acted as an excellent cathode in a fibershaped aluminum air battery.^[32]

In this work, a miniaturized sensor for the detection of Fe^{2+} and Fe^{3+} ions was developed that takes advantages of the excellent properties of CNTs along with the advantages of electrodeposited bismuth and magnetic nanoparticles. The electroanalytical performance of this unique sensor material is compared to ion detection on bare Pt working electrode surfaces in the same chip configuration. The remarkable advantage in comparison with the conventional methods such as AAS and ICP-MS is that these can measure only the total iron content. But the sensor developed herein shows the distinct detection of different iron oxidation states and the quantity of the type of oxidation states of iron present.

Results

Fabrication

The fabrication of the sensor is described in the schematic flow chart in Figure 1A. A quartz wafer of about 500 μm thickness was used as the substrate material. The wafers were subjected to piranha clean of 9:1 sulfuric acid:hydrogen peroxide at 120 $^\circ\text{C}$ prior to metal evaporation. Physical vapor deposition was carried out and 50 nm of Pt was evaporated on a

5 nm Ti seed layer by means of electron-beam evaporation. The wafers were dehydrated and primed with hexadimethyldisilazane (HDMS) and spin-coated with SPR3612 photoresist at 2000 rpm to achieve a thickness of 1.6 μm and prebaked at 90 °C for 120 s. This layer of photoresist was exposed using a mask aligner for 1.7 s followed by development and post exposure bake at 110 °C for 120 s. A UV cure of 20 min was performed before these patterned wafers were subjected to dry etching by means of Ar plasma for 10 min at a chamber pressure of 12.5 mTorr and an RF power of 100 W. The 5 nm Ti was etched using $\text{HNO}_3\text{:HF:H}_2\text{O}$ in the ratio 2:1:7 ($v/v/v$). These underwent an ashing step with oxygen plasma at 3.75 T and 450W RF power at 185 °C. A second photolithography step was performed on the wafers to open areas selectively where the Fe catalyst of 3 Å was deposited. The wafers were scribed to the individual chips and lift off was performed with acetone and subsequent 2-propanol. CNTs were grown wherever Fe catalyst was deposited in a chemical vapor deposition (CVD) furnace at 1000 °C using methane as feed gas.

PDMS molds were prepared by mixing PDMS base and curing agent in 10:1 ratio and cured thermally at 80 °C for 1 hour. Circular wells were punched in the cured PDMS and were bonded onto the fabricated sensor by means of oxygen plasma to form a confinement for the fluid sample. Figure 1B–E show the graphical representation of the modified carbon nanotubes, sensor schematic depiction, and the photographs of the fabricated sensor as a three-electrode system connected to the potentiostat, respectively.

Characterization of sensor surface

The sensor was characterized by scanning electron microscopy (SEM) and atomic force microscopy (AFM). The SEM images of Pt were taken as the control surface (Figure 2A) and show a uniform and smooth deposition of the Pt metal. Figure 2B shows an SEM image of electrodeposited bismuth on the Pt surface deposited at a constant voltage of -0.8 V that has the appearance of small grains that are uniformly deposited. Figure 2C shows the SEM image of electrodeposited ferromagnetic nanoparticles (-1.4 V for deposition on Pt) with larger crystal-like features. Figure 2D is the SEM image of the CNT grown by CVD method.

The results of the working surface with unmodified CNTs was compared to a working electrode containing CNTs modified with electrodeposited bismuth and magnetic nanoparticles (Figure 2E–H). In the co-deposition method, an electrolyte containing bismuth salt and magnetic nanoparticles and single-walled CNTs were deposited at the same time. Figure 2E shows the SEM image of the CNTs in the unmodified state and Figure 2F is the SEM image of the co-deposited surface of electrodeposited bismuth and magnetic nanoparticles and CNTs. Figure 2G–H show the modified carbon nanotubes and the close-up of the modified surface.

The SEM images show that the surface is grainy with the electrodeposited bismuth and magnetic nanoparticles and has a high surface roughness. The XRD pattern of this electrode surface of CNTs modified with electrodeposited bismuth and magnetic nanoparticles is shown in Figure 2I. The peak at 40° is attributed to Pt; 27.8° for Bi overlapped with the large background obtained from the quartz substrate and the Fe_3O_4 at 36°. The peaks for Bi and Fe_3O_4 can be confirmed with data reported from related research.^[33–36] Figure 2J shows AFM images of the CNT working electrode surface of 1 μm by 1 μm . The AFM data indicate

that the CVD grown CNTs have a forest-like appearance while the SEM of the CNTs from co-deposition has a matte-like appearance.

Electroanalytical measurement and analysis

Cyclic voltammetry was performed on individual solution containing Fe^{2+} and Fe^{3+} salts separately and then with a solution containing iron in both the above mentioned oxidation states (Figure 3). This experiment was done to study the redox reactions of Fe^{2+} and Fe^{3+} , such as the deposition and stripping peak potentials, and also to note the behavior of the two oxidation states. Figure 3A shows Fe^{2+} sulfate ion being deposited as iron metal at -1.4 V and the stripping potential at -0.754 V . In Figure 3B, the deposition of Fe^{3+} ion takes place at -1.1 V and the stripping peak potential at -450 mV . Both oxidation states show up in Figure 3C in their reduction and oxidation cycles. The stripping peak potentials identified in these cyclic voltammetry experiments were used for further optimization of the other parameters such as the holding potential and the holding time for differential pulse cathodic stripping voltammetry.

The parameters that are critical for the electroanalytical measurements were optimized prior to the calibration and sample measurements. Optimization of the holding time was done with various time periods of 30, 60, 120, 300, 600, and 900 s and were repeated three times. It was determined that holding times of 120 s and above did not have much effect nor improve the performance of the sensor (Figure 3D). This conclusion is confirmed by the plot in Figure 3E, and 120 s was sufficient to accumulate all the ions in the sample volume of $200\text{ }\mu\text{L}$. This is because there was no change in the current signal with any further increase in the holding time such as 600 and 900 s. The holding potential was varied from 1.7 V , 1.6 V , 1.5 V , 1.4 V , 1.3 V , 1.2 V , 1.1 V , 1 V , 0.9 V , 0.8 V , 0.6 V , 0.5 V , 0.4 V , and 0.3 V . The less positive potentials ranging from 0.8 V to 1.4 V gave small values of current and were not distinctive and had broader peaks. The accumulations above 1.4 V were comparatively sharper, and most importantly of higher current values with 1.5 V as the optimum potential, but then the current values started to decrease for holding potentials at 1.6 V and 1.7 V . Hence 1.5 V was used as the holding potential for the calibration (Figure 3F).

Discussion

In the first design of working electrode surface, CVD grown CNTs on the working electrode surface were used for calibration. Concentrations ranging from 0.01 mM up to 1 mM were detected on the sensor and all concentrations were measured in triplicate. ICP trace metal grade water was used for the calibration to avoid interference from other metal ions. It was found that the Fe^{2+} detection peak appears around -450 mV and the Fe^{3+} detection peak occur around -775 mV . It was determined that the limit of detection was only $1\text{ }\mu\text{M}$ for this design of working electrode. The peak positions agree with reported results, particularly the work by Van Staden and M. Matoetoe who showed Fe^{2+} and Fe^{3+} occurring at -500 mV and -800 mV , respectively.^[17] From Figure 4, we also identify the peaks occurring at -100 mV as Fe_2O_3 . This confirmed the reported work on iron oxides by the Grygar group and Dghoughi and co-workers.^[37, 38]

In the second design of the working electrode, we improved the detection limit remarkably to 0.01 nM concentration by modifying the electrode surface as previously discussed. With the help of co-deposited bismuth and magnetic nanoparticles with the CNTs, lower concentrations from 0.01 nM are clearly detectable with a drastic increase in the current values measured, thus increasing sensitivity dramatically. For instance, the 100 nM concentration gave a 52.2 μ A response, whereas previously it was measured in values below 1 μ A (Figure 4). This level of detection compares favorably to previously developed biosensors. For example, Van Staden and M. Matoetoe were able to achieve a limit of detection of 10 nM by means of their flow through cell design on a glassy carbon electrode for both Fe^{2+} and Fe^{3+} .^[7] Bobrowski et al. demonstrated a limit of detection of 7.7 nM of Fe^{3+} using their preplated bismuth film electrode on glassy carbon electrode (GCE).^[39] Gao and co-workers used carbon paste electrode modified with nafion 1,10-phenanthroline for the determination of Fe^{2+} using the differential-pulse voltammetric peak at +0.83V down to 10 nM.^[40] Van den Berg and Huang reported detection of iron in sea water using cathodic stripping voltammetry with a detection limit of 0.6 nM that gave a peak current of 5 nA.^[41] Finally, a fluoride ion-selective electrode was used by Bingyao Sun and co-workers for the potentiometric determination of iron in mineral sample with a detection limit of 20 μ M.^[42] The sensor developed in this work has a much higher sensitivity and current signal for detection in extremely low concentrations. This is most important when analyzing human samples that are available only in low sample volumes with extremely low concentrations of iron. For instance, studies have shown an increased level of iron in the bronchoalveolar lavage (BAL) of lung transplant patients.^[43] The association of infections in transplant patients and increased iron levels has not been evaluated to date. The development of an optimal sensor for these patients will require high sensitivity to detect change in iron levels at low concentrations. Currently, this sensor is being developed for the detection of iron in BAL from patients who have had lung transplants.

Conclusions

We successfully demonstrated a novel way of enhancing the sensing of iron ions using CNTs by their modification with bismuth and magnetic nanoparticles to significantly improve the limit of detection to 0.01 nM and to amplify the signal current obtained in the simultaneous detection of Fe^{2+} and Fe^{3+} with selectivity and specificity. This sensor has tremendous diagnostic potential in the field of medicine for diagnostics. Currently, this sensor is being further developed for iron detection in physiological samples and is ultimately envisioned for bedside monitoring and point-of-care diagnostics.

Experimental Section

The materials that were purchased are as follows. Quartz wafers were from WRS Materials. The materials and chemicals used in the fabrication were obtained from the Stanford nanofabrication facility and the Stanford nano-shared facilities. For experiments, ICP-MS water with ultra-trace analysis from Sigma Aldrich was used for making the different concentrations of the ions for calibration. A standard solution of Fe^{III} also from Sigma Aldrich was used for calibration. Iron(II) sulfate solution (Sigma Aldrich) was used for Fe^{II} calibration. RTU cyless silver II solution from Technic Inc. was used for silver plating for

the electrodeposition of silver. 1M KCl used for chlorodizing the silver was made from KCl salt from Sigma Aldrich. For the modified working electrode fabrication, bismuth acetate salt, magnetic nanoparticles and single-walled CNTs were purchased from Sigma Aldrich. Sylgard 184 Silicone elastomer Polydimethylsiloxane (PDMS) kit was purchased from Dow Corning.

The potentiostat used for the experiments is Interface 1000E from Gamry instruments. The sensor was connected as a two-electrode system configuration for the electrodeposition steps and a three-electrode system configuration for the other electroanalytical measurements reported in this paper.

Cyclic voltammetry was performed to study the redox reactions of the ions in the sample solutions. The sample solutions were scanned from 1.5 V to -1.5 V at a scan rate of 100 mV sec^{-1} and step size of 2 mV in unstirred conditions. In differential pulse stripping voltammetry, the working electrode surface was held at an initial potential for a specific period of time and then the potential was scanned in the negative direction. The holding potential and the holding time were optimized for the best performance of the sensor.

No deoxygenation step was performed for any of the voltammetric experiments. Before measurements of the analytes of interest, the sensor was conditioned by several voltammetric scans in ICP trace metal grade water to eliminate any of the Fe catalyst used in chemical vapor growth of CNTs coming off during the stripping step. This was done repeatedly until no more Fe from the catalyst was present on the sensor. After every 10 runs, the reference electrode was again redeposited.

For the modification of carbon nanotube electrodes, electrodeposition was performed with an electrolyte containing ($100 \mu\text{L}$ of 500 mg L^{-1} concentration) of bismuth acetate, magnetic nanoparticles ($20 \mu\text{L}$ of 1 mg mL^{-1} concentration) and CNTs at 5 mA/cm^2 current density for the electrode area.

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Figure 1.

(A) Schematic flow of sensor fabrication. After a piranha clean, 50 nm of Pt (with 5 nm seed layer Ti) is deposited on the wafers. This is followed by photolithography to form the electrode metal patterns using wet and dry etching. A second photolithography is performed to selectively expose the working electrode to Fe catalyst growth and subsequently the CVD growth of CNTs. PDMS molds formed the confinement for fluid samples. (B) Graphical representation of CNT modified with electrodeposited bismuth and magnetic nanoparticles. (C) Schematic top view of the sensor, where WE is working electrode, RE is reference

electrode and AE is auxiliary electrode. (D) Photograph of the sensor. (E) Sensor connected to potentiostat for measurements.

Figure 2.

SEM images of (A) platinum, (B) bismuth, (C) ferromagnetic nanoparticles, (D) CVD grown CNTs, (E) unmodified CNTs, (F) working electrode surface containing CNTs modified with electrodeposited bismuth and magnetic nanoparticles, (G) modified CNTs, (H) close-up of modified CNTs, (I) XRD pattern of the electrode surface with CNTs modified with electrodeposited bismuth and magnetic nanoparticles and (J) 3D AFM image of a CNT surface with 1 μm by 1 μm area.

Figure 3.

Cyclic voltammetry (CV) on Pt surface for (A) Fe²⁺, (B) Fe³⁺ and (C) Fe²⁺ and Fe³⁺ multianalyte detection. (D) Optimization of holding time with 10 μM Fe standard. (E) Calibration plot of holding time for 10 μM Fe standard. (F) Optimization of holding potential for 10 μM Fe standard.

Figure 4.

Calibration of iron with (A) cathodic differential pulse voltammetry (B) close-up of the highlighted region, (C) cyclic voltammetry at CNT working electrode surface, (D) close-up of the graph. Differential pulse stripping voltammetry for the detection of lower concentrations using (E) unmodified CNTs and (F) CNTs modified with bismuth and magnetic nanoparticles showing a marked increase in corresponding measured currents and hence detection limit.