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Dual Functional Metal Oxide Nano-materials Enabled Sensors for both Non-enzymatic Glucose and Solid-state pH Sensing

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Dual Functional Metal Oxide Nano-materials Enabled Sensors for both Non-enzymatic Glucose and Solid-state pH Sensing

Qiuchen Dong, Ph.D.
University of Connecticut, 2019

Glucose sensors play an important role in managing blood glucose level of diabetic patients. Although enzyme based glucose test strips dominate glucose detection market, the intrinsic chemical and thermal sensitivity of enzymes stimulates researchers to explore chemical and thermal metal oxides as the sensing materials for non-enzymatic glucose detection. On the other hand, pH sensor has been employed as a routine instrument in research laboratories and various industrial sectors to probe the acidity or alkalinity of aqueous solutions due to the importance of pH values for the control of water quality and chemical reactions. Although both solid-state pH sensors and metal oxide based non-enzymatic glucose sensors have been extensively and individually studied, it still remains unmet challenge to develop a single sensing material for both non-enzymatic glucose and solid-state pH sensing. This is mainly attributed to the lack of both pH-sensitive and glucose-responsive sensing materials. Therefore, new functional materials or existing materials with new functionality should be developed and/or identified in order to accomplish aforementioned dual sensor concept.

The Ph.D. project aims to synthesize, characterize, validate, and evaluate as-prepared metal oxide-based non-enzymatic glucose sensor for its glucose sensing and pH sensing by electrospun-annealing process.

The metal oxides from group 9 elements were focused in this Ph.D. project. The materials selection for glucose detection and pH sensing was based on the assumption of the metal oxide from the same group shares similar reactivity toward glucose sensing and pH detection. Our previous report found that cobalt oxide possessed both glucose oxidation and pH sensing property. Thus, this Ph.D. project focus on the exploration of
iridium oxide, rhodium oxide, and revisit cobalt oxide with improved glucose sensitivity by unique core-shell structure.

Firstly, iridium oxide oxide nanofibers were fabricated through a facile two-step method, electrospinning-annealing process. By applying scanning electron microscopy, x-ray powder diffraction and Raman spectroscopy, thermal gravimetric analysis, IrO\textsubscript{2} structure was confirmed and further applied for electrochemical characterizations. Amperometric results demonstrated good selectivity of glucose among ascorbic acid, 4-acetaminophen, uric acid, dopamine, fructose, xylose, galactose, maltose, and sucrose. Human serum sample was further adopted for clinical application assurance. In addition, amperometric tracking validated the long-term stability over 3 weeks. On the other hand, pH titration results illustrate a near-Nernst constant performance of iridium oxide as pH sensor.

In the second, rhodium oxide nanofibers were synthesized through similar electrospinning-annealing process with different curing temperature. Morphological characterizations and X-ray powder diffraction analysis validated the structure of beta-rhodium oxide structure. Electrochemical characterization further confirmed the sensitivity toward glucose and good selectivity towards aforementioned interferences. Human serum sample was also applied in amperometric experiments, reflecting potential clinical application. In addition, open circuit potential was used for pH sensing exploration, revealing sub-Nernst constant of as-synthesized rhodium oxide nanofibers.

In the third, nitrogen-doped core-shell cobalt oxide nanofibers were fabricated by coaxial needle through electrospinning and annealing two steps process and the structure was further confirmed by the analysis of X-ray powder diffraction. Transmission electron microscopy EDX metal mapping results revealed nitrogen-doped core-shell structure, providing larger surface-to-volume ratio for more active site of glucose oxidation at the interface of cobalt oxide and glucose molecules. By applying cyclic voltammetry,
hydrodynamic voltammetry, and amperometric analysis, it showed improved sensitivity and good selectivity as well as potential application in human serum sample. Afterwards, as-prepared core-shell cobalt oxide was blended with carbon paste for the modification of glassy carbon electrode. The pH titration experiments showed sub-Nernst constant.

In the fourth, both pH-sensitive and glucose-responsive heterogeneous gold-doped iridium oxide nanoparticles (IrO$_2$–Au NPs) were synthesized through electrospinning followed by high-temperature calcination. The as-prepared IrO$_2$–Au NPs were systematically characterized using various advanced techniques including scanning electron microscopy, X-ray powder diffraction and Raman spectroscopy, and then employed as a dual functional nanomaterial to fabricate a dual sensor for both non-enzymatic glucose sensing and solid-state pH monitoring. The sensing performance of the IrO$_2$–Au NPs based dual sensor toward pH and glucose was evaluated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively. The results show that the as-prepared IrO$_2$–Au NPs not only maintain accurate and reversible pH sensitivity of IrO$_2$, but also demonstrate a good electrocatalytic activity of Au toward glucose oxidation in alkaline medium at a low applied potential with a sensitivity of 21.20 $\mu$A·mM$^{-1}$·cm$^{-2}$, a limit of detection of 2.93 $\mu$M (S/N=3) and a reasonable selectivity against various interferences in non-enzymatic glucose detection. These features indicate that the as-prepared IrO$_2$–Au NPs hold great promise as a dual-functional sensing material in the development of a high-performance sensor for both solid-state pH and non-enzymatic glucose sensing.

This project pioneered the view of selecting materials for glucose sensing and pH sensing in a periodic table-directed method.
Dual Functional Metal Oxide Nano-materials Enabled Sensors for both Non-enzymatic Glucose and Solid-state pH Sensing

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APPROVAL PAGE

Doctor of Philosophy Dissertation

Dual Functional Metal Oxide Nano-materials Enabled Sensors for both Non-enzymatic Glucose and Solid-state pH Sensing

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Chapter 1

Introduction

1.1 The Background of pH Sensing & Glucose Sensing

1.1.1 The Importance of pH Sensing

Most of pH sensing and glucose sensor are based on chemical sensor device. According to IUPAC, chemical sensors are defied as “a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal” [1]. Specifically, a chemical receptor is involved in interaction of analysts, resulting in simultaneous change of physical or chemical properties. Generally, changes are recorded and can be reflected by a transducer while converting into analytical useful electric signal, and they can be processed by downstream data processing and display with proper units.

pH sensing use certain device or certain method as transducer and rely solely on hydrogen related values for monitoring hydrogen ions variation species. Measuring pH of one aqueous or pseudo-aqueous solution can offer widely information including: a. Agriculturally, spatially mapping pH profile of one large area is of paramount importance in applying fertilizer in cost-effective aspect[2]. Especially, it is necessary to investigate the pH profile spatially when soil salinization happens. b. Environmentally, acid rain pH<5 can damage constructions and buildings severely in a long term, resulting in unsafe condition of facilities and property loss. c. Medically, cancer cell will decrease the local pH value compared with normal cells, which brings researchers and doctors the opportunity to probe the appearance and location of cancer cell from early stage of development. Thus, it can benefit the welfare of human beings. Thus, pH sensing is of huge significance agriculturally, environmentally, and medically for us. Different sensing mechanisms are introduced in the following sections.
Conventional pH meter, i.e. glass pH meter used in labs, is consisted of two electrodes, including one working electrode with a fragile membrane to allow certain ions pass by and another reference electrode to correct the offset of working electrode. As-described working electrode is intended to break in terms of its low mechanical strength and to be poisoned due to high ion concentration.

Even though, pH meter is widely employed in practice both in academic and in practice, it suffers from fragile problem of glass made working and reference electrodes as well as drift issue of reference electrode in long term usage. Thus, different types of pH meter with different working mechanism and sensing materials are expected to compensate the weakness of such bulk glass pH meter for future studies.

1.1.2 The Importance of Glucose Monitoring

Diabetes is a chronic disease that occurs either when the body cannot effectively use the insulin it produces (Type 1), or when the pancreases does not produce enough insulin (A hormone that regulates blood sugar, or glucose (Type 2). Diabetes has become one of four priority noncommunicable diseases (NCDs) all over the world. The number of adults in 2014 who live with diabetes doubles it in 1980, which make it as a global issue to halt the rapid increasing. On the other hand, the high deaths rate directly with diabetes mellitus (1.5 million death in 2012) and increasing risk of having cardiovascular and other related diseases due to diabetes are making diabetes to be an urgent problem need to be solved in this century in all income countries.

These two types of diabetes both can lead to complications in many parts of body, including heart attack stroke, kidney failure, leg amputation, vision loss and nerve damage. Poorly controlled diabetes increases the risk of fetal death and other complications. The major sources of mortality morbidity are the case of blood glucose levels higher-than-optimal, or even below the diagnostic threshold for diabetes. It is set as diagnostic criterion for diabetes patients when fasting plasma glucose ≥ 7.0 mmol/L-a diagnostic-point selected on the basis of micro-vascular complications such as diabetic retinopathy. The risk of increasing blood glucose in macro-vascular disease, such as heart attack or stroke, starts before this diagnostic point. In order to have a better understanding
of the blood glucose levels on mortality, it requires us to take a look at mortality directly related to blood glucose as risk factor. The number of deaths from high blood glucose in 2012 has been estimated to 3.7 million in 2012. In such estimation, diabetes leads to 1.5 millions deaths and another 2.2 million deaths are from cardiovascular diseases, chronic kidney disease, and tuberculosis that have higher blood glucose than 7 mmol/L.

Thus far, to develop a device that can monitor and track the blood glucose on the daily base is emerging as a global problem for solving. In the market of glucose monitoring platform, intermittent track of blood glucose likewise enzyme based test strip dominates and is playing a major role in high blood glucose patients daily testing. A well-managed and detected diabetes patient can live long and healthy. Therefore, a user-friendly and easy to test point of care [3] platform are bringing increasing numbers of researchers for improving the performance of such test strip based enzymatic blood glucose monitoring.

Even though, enzymatic based test strip blood glucose monitoring has improved the diabetes patients in some extend, however, the test strip that they used are of short shelf life in terms of the intrinsic property of enzyme modified on test strip.

For better addressing such weakness of enzymatic based test strip, academically, researchers start to look into the non-enzymatic materials based glucose determination methods. Herein, this proposal will focus on the electrochemical methods glucose monitoring. It is of upmost importance for developing non-enzymatic glucose tracking system based on non-enzymatic materials platform.

Both pH sensing mechanism and glucose sensing mechanisms are summarized in next sections. One can have a big picture regarding extensive study in two fields individually. However, there is no report about measuring pH and glucose concentration at the same time as in one individual sensing system by using one material in a facile method.

1.2. pH Sensing Mechanism

pH is defined as the negative decimal of logarithm of hydrogen ion concentration. There have been several types of pH measurement instruments invented for addressing such widely measured value among agriculture, environmental, and other highly related human objects applications. Litmus paper is one of ubiquitous method to roughly
determine the pH value just by naked eye with low resolution of pH 0.1. However, it can sense from 0 to 14 wide ranges of pH aqueous situations. On the other hand, different dyes are also employed for pH sensing. Following parts will demonstrate how different performance of various types of pH sensing mechanism.

1.2.1. Optical pH Sensing Mechanism

Briefly, two different optical pH sensor sensing mechanism will be introduced herein. First, fluorescent-based pH sensor, it reveals pH related chemical property change under UV-light. Secondly, researchers develop different dye or indicator-based pH sensor.

1.2.1.1 Fluorescent-based pH Sensor

Recently, fluorescent-based pH sensors has been developed by employing metal-organic frameworks (MOFs) hybrid materials[4], gold nanoclusters[5], polypeptide[6], fluorescent protein[7, 8], synthetic platform[9, 10], etc. Different framework will be illustrated in below in sequence. The main working principle of MOFs hybrid material is that the inherent advantages of MOFs to effectively concentrate analyte molecules at higher levels to enrich the guest-host interaction, resulting in an analytical response. A moisture resistant type MOFs and a chemical resistant ability to acidic and basic environment is another prerequisite for a wide pH sensing range of fluorescent pH sensor. Hybrid materials Eu$^{3+}$@UiO-67-bpydc is synthesized and characterized for its pH sensing by tracking the fluorescence intensity at 615 nm and pH value. Gold nanoclusters are combined with pH indicator bromothymol blue (BTB) for pH sensing in terms of the emission of gold nanocluster overlap with the adsorption of BTB. The method is applied to detect the time laps of the cell death with detection range of pH 5 to 9, which cover the physiological of living cell. Thus, it makes gold nanocluster another material capable of detecting respective intracellular pH changes. As natural amino acid and an intrinsic fluorescent probe, Tryptophan (Trp) can only respond at extreme pH conditions (pH<4 and pH>9). However, N-terminal Trp-Trp dipeptides have been proved to be effective in physiological pH range as a genetically encoded pH indicator. Modified Trp-Ala-Ala-Ser (WAAS) and Trp-Glu-Ala-Ser (WEAS) were studied by substituting the second Trp by Ala and Glu, demonstrating a pH related quantum yield promising results. It can potentially used for studying pH changes of genetically encoded polypeptide. As a monomeric GFP-
like protein, Dendra2, is used for irreversible photoconvertible fluorescent protein in monitoring living cell pH changes. The chemical structure of the Dendra2 changes in the course of a photoelimination reaction. It results the fluorescence emission spectrum shifting from green to red region. Thus, the ratio of red to green color is correlated with pH changes for tracking pH in live cell. Another protein, bovine serum albumin, is croslinked with three fluorescent dyes, coumarin 460, fluorescein, and 5(6)-carboxy-x-rhodamine for pH detection. Such developed protein biophosphors is sensitive to pH from 1 to 11. For synthetic platforms, it has been reported the red-shifted chemical fluorophores derived from fluorescein-carbofluorescein (CFI) and Virginia Orange [11] to serve as probes for exo- and endocytosis tracking. CFI and VO are two newly synthesized derivatives of fluorescein. They replaced xanthene oxygen with a gem-dimethyl-carbon moiety, which resulted in the red-shifted phenomena because of oxygen→carbon substitution. It realized the intensity change with pH changes for 4-SNAP-tag conjugate in monitoring exocytosis in living cells. Coordination polymers (CPs) are another synthetic platform consisting of metal ions or metal cluster and organic ligands via covalent bonds or weak interactions such as hydrogen-bonding and π-π interactions. Even though, CPs-based fluorescent sensor has been applied for the detection of metal ions, anions, etc. it rarely is been explored in the pH sensing. The CPs-based pH sensor molecule should possess the function group that can accept H⁺ or OH⁻ without damaging the framework. Recently, researchers reported by using tmbpt ligands for the construction of CP \{Cd(2,4'-tmbpt)2](5-OH-bdc) 5H₂O(2,4'-tmbpt=1-((1H-1,2,4-triazol-1-yl)methyl)-3-(4-pyridyl)-5-(2-pyridyl)-1,2,4-triazole and 5-OH-H2bdc=5-hydroxy-1,3-benzenedicarboxylic acid\} for the sensing of pH [10]. It senses the pH changes by tracking the adsorption intensity changes at 405 nm.

Not only optical pH measurements dominate the pH sensing application field, other method, like ion sensors are especially common in academic daily use.

1.2.1.2. Dye-based pH Sensor

Colorimetric based pH indicators are widely applied in food chemistry. Researchers adopted chlorophenol red (CPR)[12] as the indicator of grapes ripeness in a package
environment. Due to the formation of sugars during berry ripening process, pH increases as with volatile organic acids decreased in the package headspace. In the duration of 30 days, the mean RGB was evaluated for the grape ripeness and the results shows that the CPR membrane can successfully be used as package indicator label for the grape ripeness.

Another widely used pH indicator is litmus test paper. It can indicate the pH with resolution as 0.5.

**1.2.2. Ion Sensors**

Most ion sensors operated by potentiometric method, which by means that the electrical potential differences are recorded in the solid/liquid interface as a function of the ion concentration. It can always be referenced by Nernst equation:

\[ \Delta \phi = RT/nF \ln \frac{a_i}{a_{i2}} \]

Here R is the gas constant, T the absolute temperature (K) and F the faraday constant, n is the number of electron involved in reaction. Ion concentrations ci are mentioned in terms of activities, \( a_i = f_i c_i \), with \( f_i \) being the activity coefficient. The equation demonstrate that, providing that at one side of the interface the activity \( a_i \) of the ion of interest is kept constant, the electrode potential is a direct logarithmic function of the ion activity on the other side. Therefore, for example, a metal electrode, likewise, copper, in its “own solution”, like, copper sulphate solution, will lead to a stable potential under no interference reaction happens. However, this kind of case can only exit ideally not realistically. To make use of a membrane of conducting glass, a well-known electrode that can buffer the ion of interest in a thin surface layer is come up with. This type of sensitive glass compositions is shaped in a bulk size and a glass shaft was used for melting onto. Such fabricated bulb contains known liquid of constant composition, serving as internal liquid. A cell, constructed with a constant potential composition, has a potential drop at the inner surface of the glass membrane and a “sensing potential” in outer surface. It can only be measured by contacting both internal solution and external solution by reference electrode. The reference electrode is consisted of a metal wire and aqueous solution for determination of the electrical potential of this solution. Practically, reference electrode is filled with a chlorinated silver wire (with coating of a insoluble
silver chloride on its surface) in a saturated potassium chloride solution. Thus, the electrochemical couple formed and results in a constant potential according to the Nernst equation. So-called frit is used for a barrier to measure the electrical potential in between inner solution and the solution that contact with. The glass membrane electrodes often are combined with reference electrode in one system.

![Cross sectional view of combined pH electrode](image)

*Figure 1.1 Cross sectional view of combined pH electrode. Reprint from reference [13]*

Figure 1.1 shows the typical schematic configuration of a glass pH electrode. It is worth noting that the sensing material, the membrane, has to be conducting for such type of potentiometric sensors in terms of the circuit has to be closed. Insulating materials, which are sensitive to ions, cannot be used. The miniaturization of such glass-membrane electrode is less stable can not be applied to in vivo monitoring in terms of its intrinsic fragile property.

Ion selective field-effect transistor is another device that is superior to ion sensors in sensitivity, which will be introduced in below.

### 1.2.3. Ion-selective Field-effect Transistor

Piet Bergveld first invented ion-selective field effect transistor (ISFET) in 1970 in University of Twente, Netherlands. An ISFET is a field-effect transistor for measuring the concentration of ion in aqueous solution. The current will change through the
transistor accordingly when the ion concentration (such as $H^+$) changes. The operation of an ISFET can be depicted by comparing it with its purely electronic analogue, the MOSFET (Metal Oxide Semiconductor Field Effect Transistor). Figure 1.2 demonstrates the similarities and differences between these two devices.

Figure 1.2 (a) Schematic diagram of a MOSFET; (b) schematic diagram of an ISFET; (Reprint from Reference [13]).

The metal gate of the MOSFET of Figure 1.2 (a) is substituted by the metal of a reference electrode, while the liquid in which this electrode is present makes contact with the bare gate insulator (figure 2(b)).

Hydroxyl groups can be appeared on any metal oxide surface, in case of silicon dioxide SiOH groups. These groups may accept or donate a proton from the solution, leaving a positively charged or negatively charged surface group respectively. Site-binding model can be used for describing the mechanism that is responsible for the oxide surface charge showed in below:

$$SiOH \Leftrightarrow SiO^- + H_B^+ \quad (1)$$

$$SiOH_2^+ \Leftrightarrow SiOH + H_B^+ \quad (2)$$

for $H_B^+$ representing the protons in the bulk of the solution. From reaction (1) and (2), one can clearly see that an originally neutral surface hydroxyl site can bind a proton from the bulk solution, thus, it becomes a positive site and donate a proton to the solution, leaving
a negative site on the oxide surface. According to the thermal dynamic equilibria and Boltzmann equations, the general expression for the pH sensitivity of an ISFET:

$$\frac{\partial \psi_0}{\partial \text{pH}_B} = -2.3 \frac{kT}{q} \cdot \alpha \text{ with }$$

$$\alpha = \frac{1}{2.3kTC_{\text{dif}}} \frac{q^2\beta_{\text{int}}}{\frac{1}{{\frac{1}{2}}}} + 1$$

Where $\psi_0$ is introduced as the difference between the potential of the oxide surface and the bulk solution, pH$_B$ is the pH in bulk solution, and, k, q, T are in normal meaning. $\alpha$ is a dimensionless sensitivity parameter that varies between 0 and 1, depending upon the intrinsic buffer capacity, $\beta_{\text{int}}$, of the oxide surface and the differential double-layer capacitance $C_{\text{dif}}$. If $\alpha$=1, the ISFET has a so-called Nernstian sensitivity of precisely -59.2 mV/pH AT 298K, which is also the maximum achievable sensitivity.

Recently, there has been a surge in research regarding EGFET in its biomedical application, due to its very suitable for built-in property. A extended-gate field-effect transistor (EGFET) has been developed based on porous n-type (111) silicon substrate used for pH sensing[14].Porous silicon was compared with a silicon wafer and realized a 56.13 mV/pH with linearity of 0.9857 (at drain-source current $I_{DS}$ of 0.1 mA, temperature of 300 K, and immersion time of 300s) performance. The silicon wafer only has 25.41 mV/pH and linearity of 0.99 under similar condition. Except for porous silicon, copper sulfate was also explored recently for its influence of annealing time on the sensitivity of EGFET pH sensor performance[15]. It was reported the maximum average grain size of the CuS membrane could be obtained at 30 min annealing time with 27.8 mV/pH sensitivity and minimum resistance of 400 $\Omega$. Not only CuS possess such good pH sensitivity towards hydrogen ion variation, ZnO/Ag/ZnO multilayers films also reflect varied electrical properties of pH sensor regards to its thickness[16]. It was demonstrated that much thickness pairs resulted in much more chemical sensitivity, linearity and hysteresis voltage.

Conventional ion sensors and ion selective-field effect transistor suffers from fragile reference as well as drift issue. Here, a differential pH sensing mechanism is spotted.
It is always an issue for whatever ISFET, ion-selective sensor to have a rugged reference electrode. Due to the fragile property of conventional reference electrode, such as Ag/AgCl (3 M KCl), is restricted for its bulky size and short-term stability. Researchers in NASA’s Jet Propulsion Laboratory, Pasadena, California invented a solid-state electrochemical sensors for measuring degree of acidity and alkalinity in 2007[17]. Theoretically, they would like to use to metal oxide solid-state electrode to measure the electric potential of working electrode and reference electrode. According to the results, iridium/iridium oxide electrode upon pH has the Nernst constant of -57〜59 mV/pH. Simultaneously, rhodium/rhodium oxide electrode upon pH was found to be a sub-Nernst constant of about -26 mV/pH. The difference between iridium/iridium oxide and rhodium/rhodium oxide has a relative 30 mV/pH value, which located within the range of typical instrumentation used in converting DC signals to digital data for recording.

![Figure 1.3 Differences Between the Potentials of an iridium/iridium oxide electrode and a rhodium/rhodium oxide electrode for the correlation of different pH values when the electrodes were in equilibrium. (Reprinted from reference [17]).](image)

Even though the results showed a relative stable Nernst constant, its potential biomedical applications are still in-need-of exploring.

1.3. Glucose Sensing Mechanism

Electrochemical based glucose detection can be divided into two categories, enzymatic and non-enzymatic glucose detections. In 1928, Muller discovered glucose 1-oxidase
[18](β-D-glucose:oxygen-1-oxidoreductase, EC 1.1.3.4). Since then, it has attracted great attentions of researchers to apply such enzyme to entrap into various developed platform. R.Wilson et al.[19] has given a good review about glucose oxidase [18] history and development. Harvesting from this review, the detailed information regarding GOD is illustrated and demonstrated. Following this review, a brief introduction of enzymatic glucose electrochemical sensor is revealed.

1.3.1. Enzymatic Glucose Sensing
In the early days, (1) glucose dehydrogenases, (2) quinoprotein glucose dehydrogenases, (3) glucose 1-oxidases, and (4) glucose 2-oxidases have been working as principal substrate initially. Glucose dehydrogenases and quinoprotein glucose dehydrogenases are both specific for β-D-glucose and have a high turnover. However, glucose dehydrogenases require a soluble NAD\(^+\) (oxidized nicotinamide adenine dinucleotide) to work and the latter is relatively unstable. These drawbacks have precluded the usage of glucose dehydrogenases and quinoprotein glucose dehydrogenases, even though they have been constructed by different researchers [20-23]. Glucose 2-oxidases [11, 24, 25] was also ruled out for wide use in terms of its ability to oxidize not only glucose but xylose and gluconolactone as well in the presence of dioxygen and with the product of hydrogen peroxide. Lacking of specificity hindered the development of such enzyme in the application of blood glucose determination. However, glucose 1-oxidase [18] (β-D-glucose:oxygen-1-oxidoreductase, EC 1.1.3.4) has been studied by a variety of researchers for its high specificity in oxidizing D(+)-glucose.

1.3.1.1. Glucose Oxidase Based Enzymatic Glucose Sensing
The Glucose 1-oxidase has been based on the production from Aspergillus niger. It has a slightly elongated globular structure[26] and with a 8 nm diameter[27] and a partial specific volume of 0.75 mLg\(^-\)1[28]. The molecular weight of glucose 1-oxidase has been reported with different value, ranging from 151×10\(^3\) to 186×10\(^3\)Da, however, most value lies in the range of 155×10\(^3\)±5×10\(^3\)Da[29]. The production of GOD was also incorporated into yeast [30] and it showed that GOD is composed of two identical subunits, and both of which are encoded with same gene.
Normally, GOD is dissolved in aqueous solution for immobilization. Thus, it is of utmost importance to understand what are the forms of glucose in water while it reaches equilibrium. Figure 1.4 shows the four types of forms of glucose present in water.

![Diagram of glucose forms](image)

Figure 1.4 The four different forms of glucose presented in water after reaching equilibrium at 293 K. GOD shows high degree of specificity towards β-D-glucopyranose form. (Reprinted from reference [19].)

It has been reported that the most effective substrate for oxidized GOD is β-D-glucose [31-33]. And that have a good corresponding catalytic role of GOD in glucose oxidation. The GOD can effectively oxidize the 63% of β-D-glucopyronose form of glucose in water after glucose reaches to equilibrium. The overall reaction of GOD involved with glucose can be expressed as listed below:

\[
C_6H_{12}O_6 + O_2 \rightarrow C_6H_{10}O_6 + H_2O_2
\]

The large enough enthalpy change associated with this reaction can be detected thermometrically and thus a number of biosensors have been come up with according
such detectable change. The reaction product gluconolactone is not stable, thus, it can further hydrolyze into gluconic acid[34].

Researchers apply electrochemical method to determine the concentration of glucose, resulting a good indication with high accuracy. Oxygen consumption and hydrogen peroxide productions are often two routes for determination of glucose involved with. In the following section, GOD-based glucose biosensor can be loosely classified as three broad classes based on their sensing mechanism, as illustrated in below.

Herein, brief introductions of three generations of glucose biosensors are listed. First generation of glucose biosensor relies on a thin layer of GOD enzyme entrapped over an oxygen electrode via a semipermeable dialysis membrane[35]. Oxygen consumption was measured for enzymatic-catalyzed reaction in below:

$$\text{Glucose} + \text{O}_2 \xrightarrow{\text{glucose oxidase}} \text{gluconic acid} + \text{H}_2\text{O}_2$$

At the same time, oxygen was reduced on the cathode electrode that follows below:

$$\text{O}_2 + 4\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O}$$

Later on, this technique was converted to a commercial product in Yellow Spring Instrument (YSI) in the year of 1975. In addition, it required a 25 µL of whole blood samples for data acquisition and processing.

In 1973, hydrogen peroxide production was measured electrochemically and used for determination of glucose concentration [36]. The reaction follows below:

$$\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}^+ + 2\text{e}^-$$

With the concept of sensing, 100 µL blood samples were required for a good accuracy and precision in wide range of amperometric enzyme electrodes.

Further development of glucose biosensor appeared in the end of 1970s’. By using electron acceptors to replace oxygen in GOD involved glucose detection [37], it steps into the second generations of glucose bio-sensing.

Third generation of glucose biosensor starts to focus on to shorten the distance of electron transfer, which is from enzyme to the active site of electrodes. It was realized by applying to use nanostructure-modified electrode and thus bring the distance of electron
travel from enzyme to the surface of the electrode shorter. Poly(pyrrole)Tetrathiafulvalene-Tetracyanoquinodimethane composite (TTF-TCNQ) has arguably reported as conducting organic salt electrode for mediatorless glucose biosensor[38-40].

After decades of development in enzymatic glucose biosensor, short-term shelf life and strict store requirements are still hinder the further future of enzymatic glucose sensor. Especially, when the temperature is higher than 40 °C° and pH <4 or pH >8, the GOD cannot work properly and thus it bring researchers to other different method for detecting glucose.

1.3.2. Non-enzymatic Glucose Sensing

Enzymatic glucose biosensor suffers from the shortage of long-term stability and shelf life due to its intrinsic property of enzyme. However, non-enzymatic glucose not only possesses good sensitivity but have excellent selectivity as well. Non-enzymatic glucose sensing exploration starts from late 90s’. Later on, mesoporous Pt has been reported with high sensitivity to overcome sluggish reaction. In addition, it realized a good selectivity with mesoporous structure among L-ascorbic acid and uric acid[41]. It became a burst after the year of 2009. In that year, Boron-doped diamond electrode was firstly reported for its promising sensitivity of 8.1 µA mM⁻¹ cm⁻² with correlation of 0.993 by amperometric method at 0.7V (vs. Ag/AgCl) of excellent selectivity among uric acid and ascorbic acid [42]. Following the clues of this paper, researchers starts to focus on improving active surface area and roughness factor to increase sensitivity and selectivity towards glucose and among different interference species, respectively. In the following sections, author will introduce the electrochemical glucose biosensor in two categories. The one is metal-based enzyme-free glucose sensing, and the other is metal oxide-based enzyme-free glucose monitoring. In terms of large amounts of research papers were published up to date, tables are used for compiling each one of kinds of materials related glucose biosensor. Related works were also briefly summarized in below.

1.3.2.1. Metal Based Non-enzymatic Glucose Sensing

Nanostructured materials have broadened the view of different dimensional structures for the glucose detection in the aspect of creating high surface-to-volume ratio, resulting
in higher sensitivity, and selectivity, respectively. Even these advantages are adopted for developing glucose biosensor in different methods; the following sections will only focus on the nanostructured materials that provide individualized catalytic effects regarding glucose sensing. For the case of metal that serves as a matrix for immobilization of enzyme [18] is not discussed here.

Up to date, enzyme-free platform of glucose biosensor has fallen into five different kinds of noble metal materials, including copper, silver, gold, nickel, palladium, and platinum with over 25, 3, 19, 23, 11, and 15 research papers, respectively. Copper and nickel acquires the most extensive investigations upon glucose detection due to its inherent high sensitivity towards glucose. Author would like to divide the metal materials of glucose sensing into two major subunits that includes group 10 metals and group 11 metals.

Group 11 metals, herein, are introduced firstly. From the point view of thermal conductivity, group 11, Cu (4.01 W/(cm K)), Ag(4.29 W/(cm K)), Au(3.17 W/(cm K)), holds even better value than group 10, Ni(0.91 W/(cm K)), Pd(0.72 W/(cm K)), Pt(0.72 W/(cm K)) under 25 °C and 1 atm, W=wat, according to CRC Handbook of Chemistry and Physics, 81st edition, 2000-2001. Even though, the glucose sensing performance is not just affected by thermal conductivity of the elements, it explain, in some extent, that the overall outstanding sensitivity of group 11.

1.3.2.1.1 Copper Nanostructure in Enzyme-free Glucose Biosensors

What copper individually serves as catalyst in direct glucose oxidation has been reported growing on varied substrate and mixed with different conducting materials, including single-wall carbon nanotube (SWCNT), multi-wall carbon nanotube (MWCNT), reduced graphene[43], graphene[44, 45], nitrogen-doped graphene[46, 47], copper foams, etc. Different substrate serves as the supporting matrix or seed layer for the growth of copper nanostructure for direct glucose oxidation. In the following section, aforementioned materials were introduced in sequence for a brief summary. Carbon nanotube is the widely used materials due to its high conductivity property and high surface to volume ratio of its three-dimensional structures. Single-walled carbon nanotube and multi-walled carbon nanotube is employed for decorating the modified glassy carbon electrode, resulting in facilitating growth of dendritic materials
formation[48], increasing electrical conductivity[49, 50], high static attraction for the in-situ growth[51] and seed-mediated by gold nanoparticle of copper growth[52].

SBA-15[53] synthesized by hydrothermal method by amphiphilic triblock copolymer/tetraethyl orthosilicate/HCl/H2O was adopted as mesoporous matrix to decorate Cu nanostructure with for direct glucose oxidation application, resulting in improved high surface to volume ratio and high capacity to include more metal nanoparticles in as well as increased number of active sites. Not only SBA-15 was able to serve such purpose, copper foams[54-56] were also applied for matrix-driven purpose in serving glucose oxidation. Other cases are listed in Table 1 in below for comparison of their direct glucose oxidation sensing performance.

Table 1 Copper nanostructure based enzyme-free glucose sensor comparisons

<table>
<thead>
<tr>
<th>Materials</th>
<th>Linear Range</th>
<th>LOD</th>
<th>Sensitivity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AuNP-CuNPs</td>
<td>0.1 µM-5 mM</td>
<td>0.03 µM</td>
<td>-</td>
<td>[52]</td>
</tr>
<tr>
<td>Cu/Ni NP-</td>
<td>0.1-5000 µM</td>
<td>2.5 nM</td>
<td>1470.2 µA mM⁻¹ cm⁻²</td>
<td>[48]</td>
</tr>
<tr>
<td>CNT/GCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu NWs-MWCNTs/GCE</td>
<td>Up to 3 mM</td>
<td>0.26 µM</td>
<td>1995 µA mM⁻¹ cm⁻²</td>
<td>[49]</td>
</tr>
<tr>
<td>Cu-nanocubes-MWCNTs/GCE</td>
<td>Up to 7.5 mM</td>
<td>1.0 µM</td>
<td>1096 µA mM⁻¹ cm⁻²</td>
<td>[51]</td>
</tr>
<tr>
<td>Cu-dendrites-SWCNH*¹/GCE</td>
<td>0.04-12.6 mM</td>
<td>17 µM</td>
<td>-</td>
<td>[50]</td>
</tr>
<tr>
<td>Cu NPs-graphene sheets</td>
<td>Up to 4.5 mM</td>
<td>0.5 µM</td>
<td>-</td>
<td>[44]</td>
</tr>
<tr>
<td>Cu/PMo₁₂-</td>
<td>0.1 µM-1.0</td>
<td>0.03 µM</td>
<td>-</td>
<td>[45]</td>
</tr>
<tr>
<td>GR/GCE*²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu-NGr*³</td>
<td>0.01-100 µM</td>
<td>10 nM</td>
<td>4846.94 µAmM⁻¹cm⁻²</td>
<td>[46]</td>
</tr>
<tr>
<td>Cu-N-G*⁴</td>
<td>0.004-4.5</td>
<td>1.3 µM</td>
<td>48.13 µA mM⁻¹</td>
<td>[47]</td>
</tr>
<tr>
<td>Cu crystals-rGO</td>
<td>0-1 mM</td>
<td>1.2 µM</td>
<td>284 mAg⁻¹ µM</td>
<td>[43]</td>
</tr>
<tr>
<td>M-SBA-15</td>
<td>10 µM-20</td>
<td>10 µM</td>
<td>63.9 µAmM⁻¹cm⁻²</td>
<td>[57]</td>
</tr>
<tr>
<td>System</td>
<td>Concentration Range</td>
<td>Current Density</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Nafion/Cu-f/GCE;</td>
<td>2-75 µM; 1 µM;</td>
<td>65.56 µA mM-1</td>
<td>[58]</td>
<td></td>
</tr>
<tr>
<td>Nafion/Cu-c/GCE *5</td>
<td>8-93 µM; 4 µM;</td>
<td>19.3 µA mM-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuNFs/MoS2</td>
<td>1-20 µM; 0.32 µM;</td>
<td>-</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>Cu NPs-leaf-extraction/GCE</td>
<td>1-7.2 mM; 0.038 µM;</td>
<td>1065.21 µAmM-1cm^-2</td>
<td>[60]</td>
<td></td>
</tr>
<tr>
<td>Cu NPs-ZnO</td>
<td>5 µM-1.1 mM; 0.3 µM</td>
<td>609.8 µA mM-1</td>
<td>[61]</td>
<td></td>
</tr>
<tr>
<td>Nanorods Array</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag@Cu yolk-shell</td>
<td>0.1-4.8 mM; 3 µM;</td>
<td>-</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td>Ag₂O</td>
<td>0.2-3.2 mM; 0.01 mM</td>
<td>298.2 µA mM-1</td>
<td>[63]</td>
<td></td>
</tr>
<tr>
<td>3-DMCus</td>
<td>0.8-3 mM; 0.8 µM;</td>
<td>3258 µAmM-1cm^-2</td>
<td>[64]</td>
<td></td>
</tr>
<tr>
<td>Polyaniline-Cu(I) composite</td>
<td>0-8 mM; 1 mM;</td>
<td>0.4744 µAmM-1cm^-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu₂O-CuO; Cu-Ni;</td>
<td>Up to 1.1 1 µM;</td>
<td>2.62 mAmM-1 cm^-2</td>
<td>[66]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Up to 1.9 mM</td>
<td>2.83 mAmM-1 cm^-2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *1SWCNH: single-walled carbon nanohorn
- *2 PO₁₂-GR: Phosphomolybdic acid functionalized graphene
- *3 NGr: Nitrogen-doped graphene
- *5: f-c: Cu nanoflowers/Cu octahedral cage
1.3.2.1.2. Silver Nanostructure in Enzyme-free Glucose Biosensors

Silver nanoparticles (Ag NPs) was reported to facilitate electron transfer for direct glucose oxidation detection. Functionalized multi-walled carbon nanotube[67], reduced graphene[67], and titatnium oxide[68], etc. were decorated with silver nanostructure, like, nanoparticles for enhanced glucose oxidation electrochemical signal. Amperometric method and differential pulse voltammetry are applied for such purpose. Table 2 lists the different materials towards glucose detection with compared sensing performance.

Table 2 Silver nanostructure based enzyme-free glucose sensing comparison

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (µAmM⁻¹cm²)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag@MH/MWCNT</td>
<td>0.0003 µM</td>
<td>1.0 nM-350 µM</td>
<td>-</td>
<td>[67]</td>
</tr>
<tr>
<td>HybridAg/Pt-NPs-rGO</td>
<td>1.8 µM</td>
<td>0.003-7.72 mM</td>
<td>129.32</td>
<td>[69]</td>
</tr>
<tr>
<td>AgNP-TiO₂</td>
<td>24 µM</td>
<td>20 -190 mM</td>
<td>3.69 mA mM⁻¹cm²</td>
<td>[68]</td>
</tr>
</tbody>
</table>

*1: MH: Metformin hydrochloride  
*2: rGO: reduced graphene oxide  
*3: NP: nanoparticles

1.3.2.1.3. Gold Nanostructure in Enzyme-free Glucose Biosensor

Electrochemical method combined with different materials including gold nanostructures has been developed for direct glucose oxidation and its detection, which contains PTCT, carbon nanotube, platinum, polypyrrole, etc. Among those materials, gold nanostructure based sensing materials can be divided into four categories. It includes gold-polymer composite, morphology controlled gold electrode, gold-carbon nanotube electrode, and boronic acid based gold electrode.

Firstly, poly 4,4,4”-tri(N-carbazolyl)-triphenylamine (PTCT) was adopted for creating gold included electrode for the consideration of its hydrogen bonding interaction and
biomimetic microenvironment, hole-transporting capability, and conductive backbone[70]. Glucose can be chemically bonded with PTCT through hydrogen bond. In addition, poly pyrrole[71] was also reported for its conducting property for improved glucose detection. Secondly, morphology-driven[72-80] gold nanostructure as sensing materials has drawn great attention in direct glucose oxidation. Improved signals were ascribed to increased active site per sensing area due to high surface to volume ratio. Considering signal amplification, mixing conducting materials such as carbon nanotube is another route to have promising signal for non-enzymatic glucose detection. Multi-wall carbon nanotube[81-83] has been reported to decorate with gold nanoparticles for such application. Last but not least, aminosilane [84] and boronic acid[85] combined with gold nanoparticles electrode served as a platform for chemical covalent bonding with glucose for detection of glucose or human serum plasma glucose were summarized herein as well.

Other cases that are not included in aforementioned are gold nanoparticles combined with metal oxides microspheres[86] and nanostructures[87]. Table 3 demonstrated a brief summary of gold nanostructure based enzyme-free glucose sensing comparison in recent 10 years.

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (µAmM⁻¹cm²)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCT/Au</td>
<td>0.2 µM</td>
<td>1.0-600 µM</td>
<td>-</td>
<td>[70]</td>
</tr>
<tr>
<td>AuNPs/CNT/IL-Nanocomposite</td>
<td>2.0 µM</td>
<td>5.0-120 µM</td>
<td>-</td>
<td>[81]</td>
</tr>
<tr>
<td>AuNPs/GCE</td>
<td>0.05 mM</td>
<td>0.1-25 mM</td>
<td>87.5</td>
<td>[72]</td>
</tr>
<tr>
<td>Pt/DGNs/GC</td>
<td>0.01 mM</td>
<td>0.1-14 mM</td>
<td>275.44</td>
<td>[73]</td>
</tr>
<tr>
<td>AuNS-DLC:P</td>
<td>300 µM</td>
<td>0.5-25 mM</td>
<td>37</td>
<td>[74]</td>
</tr>
<tr>
<td>3D-Au</td>
<td>0.5 µM</td>
<td>2 µM-1.375 mM</td>
<td>-</td>
<td>[75]</td>
</tr>
<tr>
<td>MWCNTs-COOH-poly(2-</td>
<td>3.7 µM</td>
<td>0.1-30 mM</td>
<td>1.408</td>
<td>[82]</td>
</tr>
<tr>
<td>Material/Reaction</td>
<td>Concentration</td>
<td>Range</td>
<td>Sensitivity</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>-------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>AuNPs (aminothiophenol)</td>
<td>9 µM</td>
<td>55.6 µM - 749.2 mM</td>
<td>[76]</td>
<td></td>
</tr>
<tr>
<td>Photolithography-Au</td>
<td>13.89 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbranched pine-like AuNS</td>
<td>3.39 µM</td>
<td>20-240 µM</td>
<td>776.8</td>
<td>[77]</td>
</tr>
<tr>
<td>Ppy NFs/Au</td>
<td>-</td>
<td>0.2-13 mM</td>
<td>1.003</td>
<td>[71]</td>
</tr>
<tr>
<td>AuNP-Nitrogen-doped-graphene</td>
<td>12 µM</td>
<td>40 µM-16.1 mM</td>
<td>0.25</td>
<td>[78]</td>
</tr>
<tr>
<td>AuNP-Nanotube Array</td>
<td>10 µM</td>
<td>1-42.5 mM</td>
<td>1.13</td>
<td>[79]</td>
</tr>
<tr>
<td>Boronic acid-CX-PBA—AuNPs</td>
<td>4.3 nM</td>
<td>5-100 nM</td>
<td>48.3</td>
<td>[85]</td>
</tr>
<tr>
<td>AuNPs-TiO₂ microspheres</td>
<td>-</td>
<td>1.0-15 mM</td>
<td>1350</td>
<td>[86]</td>
</tr>
<tr>
<td>Aminosilane-Assisted AuNPs</td>
<td>5 µM</td>
<td>5-50 µM</td>
<td>37.29</td>
<td>[84]</td>
</tr>
<tr>
<td>AuNP-MWCNT-poly(o-phenylenediamine)</td>
<td>0.0015 mM</td>
<td>0.05-8.85 mM</td>
<td>27.93</td>
<td>[83]</td>
</tr>
<tr>
<td>Direct Plasmon-Au</td>
<td>9.0 µM</td>
<td>0.2-23 mM</td>
<td>0.95</td>
<td>[88]</td>
</tr>
<tr>
<td>Nanocoral-(110)-Au</td>
<td>10 µM</td>
<td>0.005-30 mM</td>
<td>22.6</td>
<td>[80]</td>
</tr>
<tr>
<td>Co₃O₄/Au/FTO</td>
<td>0.1 µM</td>
<td>0.0002-0.2 mM</td>
<td>6000</td>
<td>[87]</td>
</tr>
</tbody>
</table>

Group 10 metals, herein, are introduced followed by group 11 brief reviews. It includes nickel, palladium, and platinum in this group. To be a remind that the conductivity of the elements that in group 11 are much higher than group 10, however, with improved and controlled morphology, nickel realized remarkable sensitivity towards glucose detection as well. In following section, nickel, palladium, and platinum nanostructure based materials for glucose sensing were summarized in Table 4, 5, and 6. One would able to
have a broad picture regarding sensitivity and detection limit as well as linear range of such biosensors that includes photolithography, electrodeposigon, hydrothermal synthesis, core-shell structure oriented techniques, etc for fabricating these promising sensors.

1.3.2.1.4. Nickel Nanostructure Based Enzyme-free Glucose Biosensor

Nickel nanostructure based enzyme-free glucose biosensor has attracted great attentions for glucose detection in terms of nickel itself outstanding sensitivity towards glucose. However, different types of substrate have been used to serve as a matrix for nucleation of nickel growth by hydrothermal method. For example, boron-doped diamond electrode (BDD) employed as substrate for further modification by nickel nanostructure was reported by Dai et al. and co-authors[89]. Nickel nanosheets and nanodiamonds (NDs) were electrophoretically deposited on BDD surface for stable and sensitive non-enzymatic glucose sensing. The nanodiamonds acted as nucleation sites for the subsequent of electrodeposition of Ni. It realized two linear ranges with 120 and 35.6 µA mM$^{-1}$ cm$^{-2}$ sensitivity by amperometry method. Furthermore, the hydrothermal technique also was employed for the growth of nickel nanoparticles. For instance, hydrothermal technique was applied for growth of rhizobia-like nickel nanoparticles with annealing process on Ti foil, resulting in TiO$_2$ nanowires structure. As-prepared composite arrays were used for sensitive direct glucose oxidation with 50.97 µA mM$^{-1}$ cm$^{-2}$ sensitivity and low detection of limit of 0.18 µM[90]. Not only hydrothermal technique was applied for growth of nickel nanostructures, arc plasma was adopted for the purpose of nickel modification as well. A nickel rod as cathode arc plasma source applied with 0.5 h treating under argon was prepared on pretreated glassy carbon electrode with dispersed graphene. As-prepared nickel plasma modification of graphene electrode exhibits high glucose sensitivity of 2213 µA mM$^{-1}$ cm$^{-2}$ within 1 s response time[91]. By using microwave irradiation technique, Hameed et al. [92] can use carbon Vulcan XC-72R as substrate to deposit nickel nanoparticles for glucose detection with 1349.7 µA mM$^{-1}$ cm$^{-2}$ sensitivity.

Harvesting from this carbon materials, other types of carbon nanomaterials were further explored for nickel nanomaterials involved glucose detection. Ni nanoparticle-loaded carbon nanofiber paste (NiCFP) was electrospun and annealed at high temperature. NiCFP nanocomposite was mixed with mineral oil for the construction of renewable
NiCFP electrodes for non-enzymatic glucose detection[93]. Straight multi-walled carbon nanotubes (SMWNTs) and nickel nanoparticles (NiNPs) nanohybrids were synthesized through in situ precipitation procedure for glucose detection[94]. Furthermore, Ni/multi-walled carbon nanotubes nanocomposites were successfully synthesized via a simple, rapid and efficient approach for direct glucose monitoring[95]. In addition, vertically aligned carbon nanotubes arrays with Ni-coordinated on graphite was fabricated by radiofrequency sputtering and plasma-enhanced chemical vapour deposition for glucose monitoring with ultra high sensitivity[96]. Nickel nanoparticles/graphene nanosheets (NiNPs/GNs) composites were synthesized through in situ chemical reduction procedure for synergistically effect of glucose monitoring with high sensitivity of 865 µA mM\(^{-1}\) cm\(^{-2}\)[97]. A short response of non-enzymatic glucose sensor was invented by using atomic layer deposition to fabricate carbon-nanotube-nickel (CNT-Ni) nanocomposites[98].

Another type of platform, screen-printed electrode, which has been widely applied into commercial market of glucose meter, has attracted attentions in various aspects. Disposable screen-printed nickel/carbon composites on indium tin oxide (ITO) electrodes (DSPNCE) were developed for the detection of glucose in enzyme-free platform with wide linear range from 1.0-10 mM and no interference from common physiologic interferents such as uric acid and ascorbic acid[99]. Three-dimentional porous nickel nanostructures was fabricated through in situ growing on screen-printed electrode substrate via electrochemically reducing the Ni\(^{2+}\) precursor, along with continuously liberating hydrogen bubbles. The resulting nickel-modified electrode shows extremely low detection of limit 0.07 µM with ultra high sensitivity of 2.9 mA mM\(^{-1}\) cm\(^{-2}\)[100].

Not stopping from combing carbon materials with nickel nanostructure, other materials such as polypyrrole also was given enough attentions for its large surface to volume ratio property. It has been reported that cobalt oxide nanosheets (Co\(_3\)O\(_4\) NSs)/polypyrrole nanowires (PPy NW) core-shell nano-heterostructures based on nickel foam (NF) to serve as glucose sensor with good sensitivity and wide linear range[101].

Recent trends have started to bring template-assisted method into the spotlight for researchers to explore the glucose detection. Template-directed electropolymerizations with nanopore polycarbonate (PC) were also applied by Lu et al. [102] and their group for creating highly ordered Ni nanowires arrays for glucose detection. However, template
involved methods are always tedious and time-consuming to fabricate these sensors. Thus, template-free hydrothermal growth for fabricating reduced graphene oxide/nickel/zinc oxide heterostructures on conductive glass substrate (FTO) was reported for fast electrocatalytic response (<3s) with 2030 µA mM\(^{-1}\) cm\(^{-2}\) sensitivity. The three-dimensional structure promotes lower detection of limit and it realized 0.15 µM[103]. Electrodeposition methods do provide another route for solving this. Wang et al. [104] adopted electrodeposition method by using nickel hexacyanoferrate to deposit a high degree of uniformity of nickel hexacyanoferrate (NiHCF) particles for low micromolar glucose concentration detection.

In order to bring the advantages of other materials or composites into the enzyme-free glucose sensing target, aluminum was introduced for such purpose. A single coprecipitation method was applied for Ni/Al layered double hydroxide nanosheets fabrication on Ti substrate. A wide linear range was achieved up to 10.0 mM with relatively fair sensitivity of 24.45 µA mM\(^{-1}\) cm\(^{-2}\) [105]. Similarly, NiAl-layered double hydroxides were hydrothermally synthesized on carbon cloth with nickel nitrate as nickel source. It realized an ultra high sensitivity towards glucose of 14.13 mA mM\(^{-1}\) cm\(^{-2}\). This superior sensitivity was ascribed to larger surface area and great electronic/ionic conductivity between carbon cloth and layered double hydroxide structure[106]. Pt/Ni nanostructure consisting of nano-bushes and nanocubes was fabricated onto TiO\(_2\) nanotubes for glucose monitoring[107]. Furthermore, ionic liquid as a versatile class of low melting point organic salts has been attempted for the combination with nickel nanoparticles (IL-NiNPs) for glucose monitoring[108]. Another type of Ni\(_2\)P nanoarray on conductive carbon cloth (Ni\(_2\)P NA/CC) was reported by creating a three-dimensional catalyst electrode for glucose electrooxidation under alkaline conditions[109].

Last but not least, photosensitive materials CdS was incorporated with nickel nanostructures for anti-poisoning property triggered by photoexcitation. Due to narrow band gap of CdS, Ni/CdS bifunctional Ti@TiO\(_2\) core-shell nanowire electrode showed excellent anti-poisoning under photoexcitation with high sensitivity of 1136.67 µA mM\(^{-1}\) cm\(^{-2}\) and 0.005-12 mM wide linear range as well as a low detection limit of 0.35 µM for glucose oxidation[110]. This method created a alternative method to link electrochemical
and photosensitive materials together, which could lead us to a new avenue of
electrophotocurrent sensing field.

Table 4 Nickel nanostructure based enzyme-free glucose biosensor comparison

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (μA/mM cm²)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni/NDs/BDD</td>
<td>0.05 µM</td>
<td>0.2-12 µM; 1055.4 µM</td>
<td>120; 35.6;</td>
<td>[89]</td>
</tr>
<tr>
<td>NiNPs/GNs</td>
<td>1.85 µM</td>
<td>5-550 µM; 14130; 13480;</td>
<td>865</td>
<td>[97]</td>
</tr>
<tr>
<td>Ni/Al-hydroxide-Nanostructures-Ti</td>
<td>5 µM</td>
<td>Up to 10 mM</td>
<td>24.25</td>
<td>[105]</td>
</tr>
<tr>
<td>NiAl-double-hydroxide</td>
<td>0.22 µM</td>
<td>1-329 µM; 2-279 µM;</td>
<td>14130; 13480;</td>
<td>[106]</td>
</tr>
<tr>
<td>Rhizobia-like/NiNPs-TiO₂NWs</td>
<td>0.18 µM</td>
<td>1 µM-7 mM</td>
<td>50.97</td>
<td>[90]</td>
</tr>
<tr>
<td>3D-graphene/Ni-ZnO/nanorods-Array</td>
<td>0.15 µM</td>
<td>0.5 µM- 2030</td>
<td></td>
<td>[103]</td>
</tr>
<tr>
<td>Ni-plasma-graphene</td>
<td>0.1 µM</td>
<td>1-1150 µM</td>
<td>2213</td>
<td>[91]</td>
</tr>
<tr>
<td>Ni-hexacyanoferrateNPfilm</td>
<td>1.25 µM</td>
<td>5 µM-2.5 mM</td>
<td></td>
<td>[104]</td>
</tr>
<tr>
<td>Electrospun-NiNP-CNFPaste</td>
<td>1 µM</td>
<td>2 µM-2.5 mM</td>
<td>3.3 µA/mM</td>
<td>[93]</td>
</tr>
<tr>
<td>Nano-Ni NWs-array</td>
<td>0.1 µM</td>
<td>0.5 µM-7 mM</td>
<td>1043</td>
<td>[102]</td>
</tr>
<tr>
<td>Ni NP-MWCNTs</td>
<td>500 nM</td>
<td>1 µM- 1438</td>
<td></td>
<td>[94]</td>
</tr>
<tr>
<td>Ni NPs/Carbon Vulcan X-72R</td>
<td>0.232 µM</td>
<td>Up to 1349.7</td>
<td></td>
<td>[92]</td>
</tr>
<tr>
<td>CNTs-Ni-composites</td>
<td>2 µM</td>
<td>5 µM-2.5 mM</td>
<td>1384.1</td>
<td>[98]</td>
</tr>
<tr>
<td>Ni-foam-</td>
<td>0.74 µM</td>
<td>0.7-5.0 mM</td>
<td></td>
<td>[101]</td>
</tr>
<tr>
<td>Co$_3$O$_4$Nanosheets/PPy NWs</td>
<td>mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt/Ni/TiO$_2$Nanotubes</td>
<td>0.5 µM</td>
<td>0-0.12</td>
<td>1629;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mM; 0.1-259; 10 mM;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-NiNPs</td>
<td>0.03 mM</td>
<td>0.1-20 mM</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ni/MWCNTs/GCE</td>
<td>0.05 µM</td>
<td>50 µM-10</td>
<td>45.30</td>
<td></td>
</tr>
<tr>
<td>Ni/MWCNTs/Graphite</td>
<td>30 µM</td>
<td>0.05-1.0</td>
<td>950.6</td>
<td></td>
</tr>
<tr>
<td>SPENi/Carbon composite-ITO</td>
<td>-</td>
<td>1.0-10 mM</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>3D-Ni$_2$P/Nanoarray/Conductive-carbon cloth</td>
<td>0.18 µM</td>
<td>1 µM-3</td>
<td>7792</td>
<td></td>
</tr>
<tr>
<td>3D-porous-Ni-Nanostructures</td>
<td>0.07 µM</td>
<td>0.5 µM-4.0</td>
<td>2900</td>
<td></td>
</tr>
<tr>
<td>Ni/CdSBifunctionalTi</td>
<td>0.35 µM</td>
<td>0.005-12</td>
<td>1136.67</td>
<td></td>
</tr>
<tr>
<td>@TiO$_2$Core-shell NW</td>
<td>mM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.3.2.1.5. Palladium Nanostructure Based Enzyme-free Glucose Biosensor

Palladium in the form of nanoparticles or other nanostructures was extensively explored for glucose detection, in conjunction with highly conductivity backbone materials in order to achieve high electron transfer rate. Conducting polymers were the first choice of being employed with palladium nanoparticles for glucose detection due to its well-documented conductivity. For example, Pd nanoparticles incorporated into the poly(3,4-enthylenedioxythiophene) nanofibers (Pd-PEDOTn) is reported for glucose detection with ultra low detection of limit of 0.05 µM and selectivity of 24.04 µA·mM$^{-1}$·cm$^{-2}$ [111]. Conductive carbon nanotubes were also widely used with palladium nanoparticles to achieve more sensitivity enzyme-free glucose detection. Recently, a facile spontaneous redox reaction method was employed to fabricate an electrode modified with palladium nanoparticles (PdNPs) and functional carbon nanotubes (FCNTs). As-developed electrode showed excellent resistance towards poisoning from several interferences including ascorbic acid, uric acid, and p-acetamidophenol with wide linear range up to 46
mM[112]. Furthermore, single-walled carbon nanotube (Pd-SWNTs) hybrid nanostructure was fabricated by following Pd-C (Vulcan XC-72 carbon) catalyst with minor modification. In addition, it realized a good glucose oxidation activity in neutral phosphate buffer solution pH 7.4 with a low detection of limit 0.2±0.05 µM[113].

Except carbon nanotubes, graphene oxide was brought into researchers attentions as well for developing sensitive and selective glucose biosensor. By employing a simple and environmentally-friendly ultrasonic method in an ice bath for preparation of uniform size and even distribution palladium nanoparticles on graphene oxide (Pd NPs/GO), an excellent glucose sensor was formed in a wide linear range of 0.2-10 mM[114]. In situ reduction process was employed for developing palladium nanoparticles (PdNPs)-functioned graphene (Nafion-graphene) nanohybrids. Nafion-graphene was used to adsorb Pd\(^{2+}\). In addition, hydrazine hydrate was subsequently used to reduce Pd\(^{2+}\) and thus formed PdNPs. The proposed biosensor can be applied to the quantification of glucose with wide linear range covering from 10 µM to 5 mM with a low detection limit of 1 µM[115].

Other types of fabricating method was also used Lithographically prepared faceted palladium nanoflower-modified porous carbon electrodes have 12 times increase in electrochemically active surface area over analogous planar electrodes, which achieved fast glucose responses with in 5 s and a wide linear range from 1 to 10 mM and a detection limit of 10 µM. The advantages of lithography method provided a strong adhesion in between palladium crystal structures and pyrolyzed photosresist for hundreds of cycles repeat use without noticeable current decay[116].

Porous Pd nanotubes were prepared in situ on a glassy carbon electrode for non-enzymatic glucose detection with a relatively low sensitivity of 6.58 µAmM\(^{-1}\)cm\(^{-2}\)[117]. Palladium nanoparticles were combined with other metal for glucose detection in alkaline solution. Bimetallic Cu\(_2\)O@Pd nanocomposites were facilely fabricated via the galvanic replacement reaction on glass carbon electrode for glucose sensing in alkaline solution with 19.44 µAmM\(^{-1}\)cm\(^{-2}\) of sensitivity and a low detection limit of 0.16 µM[118].

Other types of fabrications are introduced in below. A solid-liquid and solid-solid phase chemical route was used for small-sized monodisperse Pd-Ag alloy nanocrystals (NCs)
fabrication to allow Pd$_2$Ag NCs to achieve a fast electron transfer process at a modified glassy carbon electrode with a ultra wide linear range of 0.04-46 mM[119].

The next generation of palladium glucose sensor could be employ by combining electrochemical signal with luminescence. A novel electrochemiluminescence (ECL) sensor based on palladium nanoparticles (PdNPs)-functional carbon nanotubes (FCNTs) was discovered and enhanced with luminol anion (LH$^-$) by the free radicals of glucose oxidation products. It realized a detection of limit of 0.09 µM as well as resistance towards high chloride ion paired with 0.5-40 µM linear range.

Table 5 Palladium nanostructure based enzyme-free glucose biosensor comparison

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity ($\mu$A mM$^{-1}$ cm$^{-2}$)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PdNPs/poly(3,4-ethylenedioxythiophene)</td>
<td>1.6 µM</td>
<td>0.04-9 mM</td>
<td>24.04</td>
<td>[111]</td>
</tr>
<tr>
<td>Pd-CuO-galvanic replacement</td>
<td>0.16 µM</td>
<td>0.49 µM-8</td>
<td>19.44</td>
<td>[118]</td>
</tr>
<tr>
<td>ECL-PdNPs-f-CNT</td>
<td>0.09 µM</td>
<td>0.5-40 µM</td>
<td>-</td>
<td>[120]</td>
</tr>
<tr>
<td>Pd-FCNTs</td>
<td>0.46 mM</td>
<td>0-46 mM</td>
<td>11.4</td>
<td>[112]</td>
</tr>
<tr>
<td>PdNPs-graphene-hybrid</td>
<td>1 µM</td>
<td>10 µM-5</td>
<td>-</td>
<td>[115]</td>
</tr>
<tr>
<td>Lithography-3D-nanoporous-Pd</td>
<td>10 µM</td>
<td>1-10 mM</td>
<td>-</td>
<td>[116]</td>
</tr>
<tr>
<td>PdNP-GO</td>
<td>-</td>
<td>0.2-10 mM</td>
<td>-</td>
<td>[114]</td>
</tr>
<tr>
<td>PdNTs-GCE</td>
<td>1 µM</td>
<td>5 µM-10</td>
<td>6.58</td>
<td>[117]</td>
</tr>
<tr>
<td>Pd-SWCNTs</td>
<td>0.2±0.05 µM</td>
<td>0.5-17 mM</td>
<td>160</td>
<td>[113]</td>
</tr>
<tr>
<td>Pd-Ag-alloy</td>
<td>0.02 mM</td>
<td>0.04-46 mM</td>
<td>-</td>
<td>[119]</td>
</tr>
</tbody>
</table>
1.3.2.1.6. *Platinum Nanostructure Based Enzyme-free Glucose Biosensor*

For the first time, in 2003, mesoporous structures of platinum electrodes that can enhance the faradic current of a sluggish reaction was explored for non-enzymatic glucose detection of as high as 9.6 µA mM$^{-1}$ cm$^{-2}$ in the presence of high concentration of chloride ions. Later on, historically, platinum-nanotubule array electrodes (NTAEs) is systematically investigated for the glucose detection in either solution of 0.5 M H$_2$SO$_4$ or phosphate-buffered saline containing 0.1 M KCl with sensitivity of 0.1 µA mM$^{-1}$ cm$^{-2}$ and good selectivity amongst 0.1 mM p-acetamedophenol, 0.1 mM ascorbic acid, and 0.02 mM uric acid[121].

Afterwards, different substrates were employed for the growing of platinum-based nanostructures. For example, gold was used as the substrate for this purpose. Diblock copolymer surfactant template assisted Pt nanoparticles were grown onto rectangular shaped thin Au film electrode for glucose detection with wide linear range of 0.0625-22 mM[122]. Upon template assisted method, template-free method was also come up with later on. Pt nanostructures were produced for the first time by on-step template-free electrodeposition on Pt bare electrode and further demonstrated with electrocatalytic activity towards the direct oxidation of glucose[123].

Not stopping from change the substrate layer for the use of the platform, other kinds of metal or metal oxides nanostructures were combined to incorporate with platinum nanoparticles. Bimetal composite materials consisting of platinum nanoparticles decorated dendrite-like gold nanostructures on glassy carbon electrode by two-step deposition method for sensitivity glucose detection was demonstrated and it showed significantly enhanced electrocatalytic performance to glucose oxidation compared those of pure dendrite-like Au nanoparticles[73]. Constructing bimetallic hollow Ag/Pt nanoparticles [124] on reduced graphene oxide (rGO) through galvanic replacement reaction and the thermal reduction of graphene oxide, HAg/PtNPs-rGO was prepared for glucose detection with sensitivity of 129.32 µA mM$^{-1}$ cm$^{-2}$[69]. A novel Pt/Ni nanostructures consisting of nano-bushes and nanocubes was fabricated onto TiO$_2$ nanotubes. It realized two linear ranges for detection of glucose from 0-0.12 mM and 0.1-10 mM with sensitivity of 1629 and 259 µA mM$^{-1}$ cm$^{-2}$[107].
Except metal/metal oxides, conducting polymer was applied for the entrapment of Pt due to the enrichment of amine group on the surface. For instance, Polydopamine (PDA) coatings are a promising route multifunctional platforms for decorating various materials, however, electrochemical polymerization of dopamine (EPD) is reported for a time-saving strategy. Owing to the abundant catechol and amine groups in the PDA layer, uniform Pt nanoparticles (NPs) are deposited onto TiO$_2$ nanotube arrays (NTAs). Such-developed materials was applied for electrochemically detect glucose with detection of limit of 0.02 mM [125]. Furthermore, a rapid, one-pot, nontoxic and template-free method was used to fabricate platinum nanoflower on graphene oxide to realize non-enzymatic glucose detection with relatively low sensitivity of 1.26 µA mM$^{-1}$ cm$^{-2}$ [126].

As the development of the non-enzymatic glucose sensor detection, researchers started to focus on the human serum or whole blood sample glucose detection. Park et al. [127] and their co-authors developed a nanoporous Pt electrode for continuous glucose monitoring in 100% human whole blood and serum system for maintaining 7 hours working function under constant electrified condition. This is the first paper that using 100% whole blood and serum for the real glucose in blood monitoring. The unprecedented long-term stability provides an alternative to conventional enzymatic glucose sensors. Furthermore, a more near clinical application research was reported as well. Patch-shaped micro-needle with Pt black sensing electrode was developed for painless continuous glucose monitoring with sensitivity of 1.62 µA mM$^{-1}$ cm$^{-2}$ [128].

On the other side of electrochemical glucose detection, photocatalytic performance of some materials paired with platinum electrodes were developed as well. Hsu et al. [128] relied on illumination method to enhance the glucose detecting performance. Hydrothermally grown ZnO nanowires on a glass substrate and decorated with Pt nanoparticles to fabricate the working electrode for a non-enzymatic glucose biosensor showed remarkable sensitivity of 928.1 µA mM$^{-1}$ cm$^{-2}$ and 123.0 µA mM$^{-1}$ cm$^{-2}$ under UV and green light emitting diodes, respectively. The UV/green light used here was to enhance signal by reducing the Schottky barrier and localizing the surface plasmonic resonance effect under illumination. In addition, Song et al. [129] firstly reported that UV light can be used photocatalytically to self-cleaning poisoned Pt particles to re-establish activity of catalytic Pt particles.
Paired with photocatalytic materials, platinum will gradually have more studies regarding combination of electrochemical and photocatalytic property.

### Table 6 Platinum nanostructure based enzyme-free glucose biosensor comparison

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (µAmM⁻¹cm⁻²)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PtNanoflowers-GO</td>
<td>2 µM</td>
<td>2 µM-20.3 mM</td>
<td>1.26;0.64;</td>
<td>[126]</td>
</tr>
<tr>
<td>PtNPs-dendrite-like-AuNPs/GCE</td>
<td>0.01 mM</td>
<td>0.1 mM-14 mM</td>
<td>275.44</td>
<td>[73]</td>
</tr>
<tr>
<td>Pt-black-Micro-Needle</td>
<td>50 µM</td>
<td>Up to 36 mM</td>
<td>1.62 µA/mM</td>
<td>[128]</td>
</tr>
<tr>
<td>ZnO NWs/Pt</td>
<td>-</td>
<td>Up to 15 mM</td>
<td>928.1;123;</td>
<td>[130]</td>
</tr>
<tr>
<td>Electrified NP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[127]</td>
</tr>
<tr>
<td>TiO₂ NT-Pt NPs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[129]</td>
</tr>
<tr>
<td>PtNPs-Carbon-nanocubes</td>
<td>-</td>
<td>1-100 µM</td>
<td>26.002±0.01</td>
<td>[131]</td>
</tr>
<tr>
<td>Ag-Pt-HollowNPs-rGO</td>
<td>1.8 µM</td>
<td>0.003-7.72 mM</td>
<td>129.32</td>
<td>[69]</td>
</tr>
<tr>
<td>PtNPs-Au-thin-Film</td>
<td>-</td>
<td>0.0625-22 mM</td>
<td>0.32 µA/mM</td>
<td>[122]</td>
</tr>
<tr>
<td>Pt/Ni/TiO₂NT</td>
<td>0.5 µM</td>
<td>0-0.12 mM;</td>
<td>1629;</td>
<td>[107]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1-10 mM</td>
<td>259;</td>
<td></td>
</tr>
<tr>
<td>PtNP-TiO₂NT</td>
<td>0.02 mM</td>
<td>0-4 mM</td>
<td>56</td>
<td>[125]</td>
</tr>
<tr>
<td>PtNanopetals-Nanosheets</td>
<td>-</td>
<td>-</td>
<td>51.6±10.8</td>
<td>[123]</td>
</tr>
<tr>
<td>PtNT-Arrays</td>
<td>1.0 µM</td>
<td>2-14 mM</td>
<td>0.1</td>
<td>[121]</td>
</tr>
<tr>
<td>Pt-mesoporous</td>
<td>-</td>
<td>-</td>
<td>9.6</td>
<td>[41]</td>
</tr>
</tbody>
</table>
To this end, metal based enzyme-free glucose biosensors have been well documented, from the aspect of sensing materials, performance, thus, one can conclude metal nanostructures combined sensors are of paramount sensitivity for direct glucose oxidation, and low detection limit compared with healthy physiological human blood glucose concentration, as well as wide linear range. However, it is obvious that most of sensors suffer from near-neutral sensing environments, instead, they all only can work in pH 13 electrolyte or 0.1 M NaOH solutions except platinum and [110] plane gold, which restrain its commercialization of real application. It is worth to mention that sensors included gold and platinum nanostructure has the ability to have relative comparable sensitivity in pH 7.4 solution or phosphate buffer saline environments.

1.3.2.2. Metal Oxides Based Non-enzymatic Glucose Sensing

According to the data from World Health Organization (WHO), the number of adults living with diabetes has quadrupled from 1980 to nowadays, reaching 422 million. Regardless of income level, diabetes has become prevalent globally, markedly in world’s middle-income countries. There are two main types in this disease - Type (I) caused due to lack of insulin production by pancreatic islet cells and Type (II) caused due to underutilization of insulin produced in the pancreas by the body. While it is a chronic disease, diabetes can lead to complications and severe symptoms, responsible for a significant number of deaths (e.g., 1.5 million deaths in the year of 2012). Extensive research on diabetes management shows that stringent blood glucose monitoring can delay the onset and progression of diabetes related complications and lower the diabetes associated mortality significantly.[132, 133] Thus, it is always a high demand to develop affordable and accessible medical care instruments and protocols for diabetes patients to monitor and self-manage their blood glucose level. In general, two major methods to manage diabetes are through intermittent glucose measurement and continuous glucose monitoring system. Currently, enzymatic based test strips glucose biosensor, including glucose oxidase and glucose dehydrogenase enzyme, have occupied almost 85% of the market by intermittently finger pricks test. Alternatively, continuous glucose biosensors are of advantages of real-time measuring glucose level in vivo, thus generating instant
glucose level information for timely decision of treatment. Practically, implantable glucose biosensors are used to realize continuous monitoring of glucose. For the consideration of implantation, the materials that are applied for in vivo glucose determination have to be biocompatible and biodegradable due to stringent requirement for implantable device.[134] Moreover, implantable devices have to be able to overcome “foreign body” response due to long-time period of exposure to subcutaneous tissue. Consequently, in vivo continuous glucose detection only reaches moderate success. As a comparison, in vitro monitoring device involving glucose test trips and a handheld glucose monitor, still possesses unprecedented merits towards blood glucose monitoring.

Although various methods have been developed for the determination of glucose in vivo or in vitro, including fluorescent carbon dots based fluorescent method,[135] photoacoustic resonance,[136] optical method,[137] up-converting glasses based method,[138] Raman spectroscopy,[139, 140] metal oxides based field-effect transistor,[141] etc., electrochemical-based (bio)sensors[142-148] possesses unbeatable low-cost, selectivity, sensitivity and portability. Therefore, this thesis will discuss electrochemical glucose sensors with a main focus on metal oxide based non-enzymatic glucose sensors.

Historically, since the first commercialized glucose biosensor was released by Yellow Spring Instrument Inc. (YSI Inc.) in 1975, enzymatic glucose biosensor has gone through three generations and its performance has been significantly improved with the use of mediators for electron transfer or the use of nanomaterials for direct electron transfer, which has been summarized in a recent review.[149] However, the intrinsic instability of enzyme and the requirement of mild operating/storage conditions[19] could sacrifice the shelf life and the sensing performance of the glucose sensing strips. Therefore, it is of high necessity to develop non-enzymatic glucose sensors as an alternative to overcome some intrinsic disadvantages of enzyme, such as pH- and temperature-dependent activity and especially the loss of enzyme functions in extreme environment. Up to date, metal, metal-alloy, metal hydrate, metal sulfate, metal nitrides, and metal oxide have been extensively studied for their glucose oxidation capability both in neutral and alkaline
environment. Among them, metal oxides have been receiving extensive attentions in electrochemical glucose sensing due to their superior stability and easier accessibility than metals or metal-alloys. Specifically, the oxides made of elements from group 7, 8, 9, 10, 11, 12 in Periodic Table have been extensively investigated for high-performance non-enzymatic glucose monitoring in last decades, which will be systematically reviewed in this article. This thesis begins with the sensing mechanism and working principles of metal oxides based glucose sensors. Moreover, the recent progress of the metal oxide based non-enzymatic glucose detection technique is discussed and, finally, this thesis will be concluded with a discussion of future trends in the development of advanced non-enzymatic glucose sensors.

1.3.2.2.1. Mechanism of Metal Oxide Based Glucose Sensor

1.3.2.2.1.1 Metal Oxide Molecules Attacked by Hydroxide Ions

Metal oxides based glucose sensing mechanisms has been systematically investigated. Most of them relies on the attacking of hydroxide ions with the metal oxides surface which then serves as catalyst for glucose oxidation, thus forming MO₄OOH (M=metal, such as Cobalt). Such intermediate can be further reduced back to MO₃ again as to be reversible in direct glucose oxidation. For example, Co₃O₄ is presumably react with hydroxide ions to form CoOOH which is further converted to CoO₂. Finally glucose reacts with CoO₂. The mechanism can be illustrated in following equations:

\[ \text{Co}_3\text{O}_4 + \text{OH}^- + \text{H}_2\text{O} \rightleftharpoons 3\text{CoOOH} + e^- \]
\[ \text{CoOOH} + \text{OH}^- \rightleftharpoons \text{CoO}_2 + \text{H}_2\text{O} + e^- \]
\[ 2\text{CoO}_2 + \text{C}_6\text{H}_{12}\text{O}_6 \text{(glucose)} \rightarrow 2\text{CoOOH} + \text{C}_6\text{H}_{10}\text{O}_6 \text{(gluconolactone)} \]

Similarly, nickel oxide (NiO) also follows the similar reaction route as cobalt oxide, but NiOOH directly reacts with glucose.[150, 151]
\[ \text{NiO} + \text{OH}^- \rightarrow \text{NiOOH} + e^- \]
\[ 2\text{NiOOH} + \text{glucose} \rightarrow 2\text{NiO} + \text{gluconolactone} + \text{H}_2\text{O} \]
In the case of copper oxide (CuO), following mechanism is proposed for glucose detection:[152]
\[
\text{CuO} + \text{OH}^- \rightarrow \text{CuOOH} + e^- \\
\text{CuO} + \text{H}_2\text{O} + 2\text{OH}^- \rightarrow \text{Cu(OH)}_4^- + e^- \\
\text{Cu (III)} + \text{glucose} \rightarrow \text{gluconolactone} + \text{Cu (II)}
\]

As for manganese oxide (MnO$_2$) toward glucose sensing[153], following equation dominates the reaction:
\[
2\text{MnO}_2 + \text{C}_6\text{H}_{12}\text{O}_6 (\text{glucose}) \rightarrow 2\text{MnOOH} + \text{C}_6\text{H}_{10}\text{O}_6
\]

In a brief summary, Co$_3$O$_4$, CuO, Cu$_2$O, MnO$_2$, composite of NiCo$_2$O$_4$ [148] etc. all share the similar sensing mechanism, which include one or all processes of (1) the attacking by hydroxide ion; (2) the formation of intermediates serving as catalyst for glucose oxidation; and/or (3) intermediates are reduced back to original form of metal oxide. The hydroxide ion involved sensing mechanism typically requires basic pH environment (e.g., pH 13) in all aforementioned articles, which may limit their clinical application as clinical detection would prefer the electrolyte to be around pH 7 or neutral.

**1.3.2.1.2. Metal Oxide Being Functional in Neutral pH**

Apart from aforementioned metal oxides, ferric oxide[18] shows promise for glucose detection at neutral pH. Following reaction is occurred first on the surface of ferric oxide.
\[
\text{Fe(III)} + \text{OH}^- \leftrightarrow \text{Fe(II)OH} + e^-
\]

However, while it served as glucose catalyst, it follows the sensing mechanism proposed below:
\[
2\text{Fe (III)} + \text{glucose} \rightarrow 2 \text{Fe (II)} + \text{gluconolactone} + \text{H}_2\text{O}_2 \\
\text{gluconolactone} + \text{H}_2\text{O} \rightarrow 2\text{H}^+ + \text{gluconate} \\
2\text{Fe (II)} \rightarrow 2\text{Fe (III)} + 2e^-
\]

Amazingly, ferric oxide, thus far, was the only metal oxide that has been reported to possess the non-enzymatic property toward glucose in the neutral pH without the help of UV light exposure. Surprisingly, there were less literatures focusing onto ferric
oxide. Recently, a composite material of highly selective Fe@ZnO was synthesized by a simple annealing process and drop-cast onto the screen-printed electrode for non-enzymatic glucose sensing at neutral pH 7.4. Such sensor held good selectivity against ascorbic acid, dopamine, and uric acid with the limit of detection of 0.13 µM. In addition, the difference of peak current in cyclic voltammetry between SPE/ZnO and SPE/Fe@ZnO in the presence of 5 µM glucose further confirmed the importance of Fe in improving glucose detection at neutral pH. Other researchers, not from the field of non-enzymatic glucose sensing, might well greet it with a shrug, but that may itself be a kind of victory, or at least a turning point. From the point of view of in vivo monitoring or long-term glucose monitoring, ferric oxide might be a promising candidate in the field of non-enzymatic glucose sensing, however, more work is required to fully understand its unique glucose sensing performance.

1.3.2.1.2 Metal-Metal Oxide Interface Formed Schottky Barrier

Another glucose oxidation mechanism depends on the wide band gap of intrinsic property of metal oxide, such as titanium oxide, nickel oxide and zinc oxide (3.37 eV). This kind of metal oxides can form the Schottky barrier on the interface of metal oxide when contacting with metal, such as Pt[129, 130] or Au.[155] For example, Wang et al. [155] introduced the concept of Schottky interface as a novel strategy for constructing non-enzymatic glucose sensor by sputtering gold onto nickel oxide, which was produced by annealing nickel foam. Consequently, the Schottky barrier was formed at the interface. Before the contacting of NiO with Au, its energy band was displayed as in Fig.1a, which is large. However, after contacting with Au, the Schottky barrier formed and labeled as $\varphi_{SB}$ in Fig. 2b. When glucose loses one electron in terms of oxidation to form electroactive intermediates in sodium hydroxide solution, it becomes positively charged molecules and induces negative charges (Fig. 1d), resulting in $\Delta \varphi_{SB}$ and the increased Schottky barriers. Owing to the increased Schottky barrier, the energy band was correspondingly decreased, accomplishing the electrons transferred from Au to NiO with lower energy to overcome.
Such mechanism of Schottky barrier may also be one of the factors in enhancing the sensing performance observed in our previous study of Au-NiO based non-enzymatic glucose sensor, but the effect of Schottky barrier was not discussed.[156] Therefore, Schottky interface should be considered in the electrochemical non-enzymatic glucose sensing in order to explicate the sensing mechanism of doping noble metal in metal oxides.

Figure 1.5. The energy band diagram of Au and NiO before contact (a), after contact (b), after absorbing positively charged molecules (d), and (c) The pathway of electrons transport. Reprinted with permission from reference.[155]

1.3.2.1.3. Metal Oxide for Mimicking Glucose Oxidase to Catalyze Glucose into Hydrogen Peroxide and Gluconolactone

The third mechanism is to mimick glucose oxidase activity with the aid of UV light and decomposes glucose into hydrogen peroxide and gluconolactone. The latter is further decomposed into gluconic acid. Zinc oxide is the only material that holds such function so far, to the best of our knowledge. Specifically, Sarangi et al. and Mai et al.[157] [158] reported separately based on the idea that ZnO nanorods under UV light can decompose glucose into gluconic acid and hydrogen peroxide, as shown in Fig. 2. The glucose
concentration was correlated with the intensity of photoluminescent (PL) in a reciprocal relationship, indicating that higher concentration of glucose incubated with ZnO nanorods resulted in lower PL intensity.

\[
\text{Glucose} + O_2 + H_2O \xrightarrow{\text{UV light}} \text{ZnO Nanorods} \quad H_2O_2 + \text{Gluconic acid}
\]

Figure 1.6. Suggested PL quenching mechanism of glucose-treated ZnO nanorods.

As a summary, three major types of metal oxides sensing mechanisms were summarized for non-enzymatic glucose determination in aforementioned section. The realization of metal oxides based non-enzymatic glucose sensing at neutral pH holds the great potential for \textit{in vivo} clinical applications.

1.3.2.2.2 Non-enzymatic Based Metal Oxide Glucose Sensor

1.3.2.2.2.1 Copper Oxide/Cuprous Oxide Enzyme-free Glucose Sensor

As early as in 1989, a pioneering study of Cu (II) modified glassy carbon electrode was reported to oxidize to Cu(III) and applied for carbohydrate detection, such as mono- and disaccharides by employing electrochemical methods in alkaline environment.\cite{159} Relying on the sensing mechanism of metal oxide attacked by hydroxyl radicals to form active site (CuO•OH), Xie and Huber et al. \cite{160} reported that Cu₂O and carbon paste modified glassy carbon electrode possessed carbohydrate oxidation catalytic activity in 0.1 M NaOH. However, the as-modified glassy carbon electrode did not have the ability to distinguish different kinds of carbohydrates. Following previous works, You et al. \cite{161} reported the superior catalytic property of 4.5% CuO/Cu(OH)₂ than 2.6% of copper
oxide/hydroxide nanoparticles with carbon film by co-sputtering copper and carbon at the same time. The results indicate that a higher amount of CuO/Cu(OH)$_2$ is responsible for a higher electrooxidation sensitivity toward glucose. Furthermore, Batchelor-McAuley et al.[162] arguably reported that CuO nanoparticle had the effect instead of arc-multiwalled carbon nanotubes (made of arc discharge method and free from metal nanoparticle catalyst) for glucose electrooxidation in alkaline environment. Through these studies, the sensing mechanism of CuO or Cu$_2$O toward mono- or disaccharides has been greatly explored and validated. The necessary step of sensing glucose involved with the attacking of absorbed hydroxyl and the formation of Cu$_x$O•OH intermediates, which serve as catalysts for carbohydrates oxidation at certain applied potential in aqueous alkaline environment.

Since then, abundant literatures about copper oxide and cuprous oxide based non-enzymatic glucose sensing mainly focus on improving the sensitivity, the linear range[163], the lower limit of detection, and the selectivity against ascorbic acid, uric acid, dopamine, fructose, lactose, xylose, galactose, maltose, sucrose, etc.. Up to date, various kinds of methods have been exploited for enhancing sensitivity, including the use of multiwalled carbon nanotube[164], graphene[165-167], reduced graphene oxide[168, 169], graphene oxide[170], and Vulcan XC-72[171]). The strategies such as increased surface to volume ratio of various copper oxide[167, 172-181] and incorporation of conducting polypyrrole with reduced graphene oxide [182, 183] were also explored. These studies further validated the sensing mechanism involved the hydroxide ion first attacking copper oxide, followed by glucose oxidation triggered by intermediates of Cu$_x$O•OH.

For the consideration of portability and in vitro test strip fabrication, Ink-jet printing technique was applied for CuO modification on printed Si/Ag substrate for the first time by Ahmad et al.. [163] Several other groups also reported to print CuO on Ag pattern[184] with Ag ink or on Au thin film [185] for non-enzymatic glucose detection. Inspired by intrinsic micropores/mesoporous structure, the desilication by base leaching of MFI zeolite was adopted for creating mesopores (10-30 nm) for the immobilization of
the CuO nanoparticles with high loading and thus applied for non-enzymatic glucose determination in alkaline environment. Furthermore, quantum dots were also exploited for improving the sensing performance of Cu₂O non-enzymatic glucose sensor. Even though the exact mechanism of quantum dots combined with Cu₂O in promoting redox reaction processes and electrochemical glucose detection was still not fully understood, the results show that doping quantum dots did make such non-enzymatic glucose sensor superior to the peer with use of just Cu₂O.[186]

Other than aforementioned methods using copper oxide or cuprous oxide with different morphologies of, titanium oxide was also utilized in the combination with CuO for enzyme-free glucose detection. Because of the well alignment of two-dimensional TiO₂ nanotube/nanofibers structure, it provided a large surface area for copper oxide decoration in electrochemical sensing. Different strategies such as anodization of Ti substrate,[187] electrospinning-annealing process,[188] and so-gel manufacturing process described elsewhere[189] have been used to incorporate titanium oxide with copper oxide in non-enzymatic glucose determination. In these scenarios, titanium oxide did not provide any catalytic activity toward glucose oxidation in alkaline environment, but enhanced the sensing performance by anchoring more copper oxide or cupric oxide nanomaterials with good accessibility.

Recently, there is a growing trend to synthesize copper hydroxide materials as a substitute for copper based oxides in non-enzymatic glucose determination. The Cu(OH)₂ in conjunction with reduced graphene oxide (rGO) was prepared by a simple hydrothermal process and applied by Jiang et al. [190] for non-enzymatic glucose detection with an impressive sensitivity of 3320.3 µA mM⁻¹ cm⁻².

1.3.2.2.2 Nickel Oxide Non-enzymatic Glucose Sensor

Nickel oxide has also been extensively studied for their non-enzymatic glucose oxidation property in alkaline solution. Carbohydrates oxidation on nickel oxide were studied by electrooxidizing the corresponding metal hexacyanoferrate to nickel oxide through cyclic
voltammetry, followed by replacing electrolyte with 1 M NaOH or KOH for 25 times.[191] The cyclic voltammetry was further applied for carbohydrates such as glucose, sucrose and xylose, further proving the glucose catalytic property of nickel oxide on the glassy carbon electrode. Following the study of nickel oxides in alkaline environment for carbohydrates determination, Shamsipur et al. [192] reported an electrooxidation method to deposit nickel oxide on top of multi-walled carbon nanotube and the modified glassy carbon electrode was applied for glucose detection in alkaline environment. Although relative low performance (the limit of detection of 0.16 mol/L and the linear range from 0.2 mol/L to 12 mol/L) was achieved, this is seminal research using nickel oxide for glucose detection. Nearly at the same time, another group[193] reported a method to prepare nickel oxide on fluorine tin oxide (FTO) through electrospinning of nickel nitrate nanofibers (NiO NFs) in polyvinylalcohol (PVA) followed by high-temperature annealing. The sensing electrode was further applied for electrochemical detection of glucose concentration through direct glucose oxidation in alkaline environment. The as-prepared NiO NFs catalyst displays a great sensitivity of 1785.41 µA mM⁻¹ cm⁻² and a superior limit of detection of 33 nM. Afterwards, a range of nickel oxide nanomaterials with different noble metal dopants prepared through the process of electrospinning and annealing were employed for glucose detection. Ding et al.[156] reported that doping of gold and other noble metals into nickel oxide can enhance the glucose sensing performance, compared to pristine NiO itself, demonstrating the synergistic effects between the dopants and NiO. Although the good selectivity of NiO doped with noble metal toward glucose against uric acid and ascorbic acid, the effect of other sugars such as xylose, galactose, sucrose, and maltose on glucose sensing is unknown.

The other widely explored functional materials in NiO are reduced graphene oxide and mesoporous carbon. For instance, by following Hummers method to prepare graphene oxide,[194] Zhang et al.[195] improved the performance of electrospun-annealed NiO by casting it onto reduced graphene oxide, resulting in high-performance non-enzymatic glucose sensor in alkaline solution. The sensing mechanism was proposed as the electron transfers between Ni (III) and Ni (II) species, accompanying with glucose oxidation. The
as-prepared sensor possesses the sensitivity of 1100 µA mM⁻¹ cm⁻² with the limit of detection of 0.77 µM, which is slightly inferior to the one prepared by the same electrospun-annealing method that previously reported by Cao et al.[193] Furthermore, hydrazine hydrate was used for in situ reduction of Ni²⁺ in the presence of commercialized graphene oxide, thus forming a composite consisting of reduced graphene oxide and the mixture of Ni/NiO[196] for non-enzymatic glucose sensing. The disadvantage of this method was time-consuming for material preparation. Another kind of carbon material, ordered mesoporous carbon (OMC), was also synthesized and cast onto the surface of the glassy carbon electrode first. The nickel oxide was electrodeposited onto the aforementioned layer of OMC at an applied potential of -1.1 V, resulting in a nickel (II) oxide/OMC modified electrode (NiO/OMC/GCE) for glucose sensing. In addition, nitrogen-doped carbon nanofibers were prepared by electrospinning technique with the mixture of polyacrylonitrile (PAN) and dimethyl dimethylformamide (DMF) followed by a drying and annealing process, and finally went through a stabilization process in high-purity nitrogen atmosphere.[197] The as-prepared nitrogen-doped carbon fiber were mixed with nickel nitrate hydrate for the formation of NiO-decorated carbon fibers after an annealing process. The sensing performance of the as-prepared NiO with nitrogen-doped carbon nanofibers towards glucose was evaluated in alkaline environment and the response displayed a linear range up to 10 mM glucose.

Metal-Organc-Framework (MOF) was also first prepared by employing nickel mesh as the precursor and reacting with L-aspartic acid and 4,4’-bipyridine to form a seed layer, followed by the secondary growth at 150 °C for 2 days in a mixture with a ratio of 1.0 bipy: 0.9Ni(L-asp): 333H₂O: 263CH₃OH. Finally, the as-prepared MOF membrane was annealed at 500 °C for 2 h under atmosphere to obtain the 3D NiO layer electrode[198], which shows a relative high sensitivity of 478.9 µA mM⁻¹ cm⁻² and a limit of detection of 4.34 µM.

Besides the aforementioned metal oxides, metal oxides made from group 9 elements, cobalt, iridium and rhodium, have also brought a great deal of attentions in the development of non-enzymatic glucose sensors since the pioneering work conducted by
Ding et al. [199] The following sections will cover the discussion on cobalt oxide, iridium oxide and rhodium oxide based non-enzymatic glucose detection.

1.3.2.2.3. Cobalt Oxide Non-enzymatic Glucose Sensor

Electrospinning has been employed as a facile method to synthesize metal oxide nanofibers,[200] however, the application of cobalt oxide nanofibers for glucose determination was not revealed until Ding et al.[199] reported a cobalt oxide based non-enzymatic glucose sensor. In this study, cobalt oxide nanofibers were prepared by electrospinning the mixture of polyvinylpirrolidine (PVP) and cobalt nitrate, followed by high-temperature calcination. Amperometric detection of glucose using the as-prepared cobalt oxide nanofibers was demonstrated with good selectivity and sensitivity (36.25 µA mM$^{-1}$ cm$^{-2}$). The sensing mechanism was proposed as the attacking of hydroxide ions on Co$_3$O$_4$ to form CoOOH, which further reacts with hydroxide ion to generate CoO$_2$ for glucose oxidation. In another study, acicular cobalt oxide was prepared by chemical bath deposition followed by pyrolysis and annealing process and then used as catalysts for glucose oxidation.[201] A similar sensing mechanism was proposed that included the conversion of Co(IV) to Co (III) in the presence of glucose.

Following these seminal studies, other three dimensional morphological cobalt oxides were formed on different matrix such as leaf[202], cobalt-based metal-organic framework (Co-MOF) template,[203, 204] egg-shell membrane matrix,[205] Pongam seed shells-derived activated carbon matrix,[206] and ordered mesoporous carbon matrix,[207] thus introducing more surface area to incorporate cobalt oxide nanomaterials. Table 1 summarizes the sensing performance of different cobalt oxide synthesized on different template matrix.

Table 7 Comparison of glucose sensing performance varied with various matrixes

<table>
<thead>
<tr>
<th>Materials</th>
<th>Detection of limit (µM)</th>
<th>Linear Range (mM)</th>
<th>Sensitivity µA mM$^{-1}$ cm$^{-2}$</th>
<th>Applied Potential</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co$_3$O$_4$-OMC</td>
<td>1.0</td>
<td>0.01-0.8</td>
<td>2597.5</td>
<td>+0.55 V</td>
<td>[207]</td>
</tr>
<tr>
<td>Material</td>
<td>Sensitivity</td>
<td>Limit of Detection</td>
<td>Potential (V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>--------------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaf-templated 3D Co$_3$O$_4$</td>
<td>0.1; 0.001-0.3; 471.5;</td>
<td>+0.59 V</td>
<td>[202]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$-hollow-nanododecahedra-Co-MOF</td>
<td>0.24; 4-12.5; 389.7;</td>
<td>+0.55 V</td>
<td>[203]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg-membrane matrix-3D-hierarchical-porous-Co$_3$O$_4$</td>
<td>0.58; 0.002-6.06; 708.4;</td>
<td>+0.55 V</td>
<td>[205]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pongam seed shells-derived activated carbon (PSAC)-Co$_3$O$_4$</td>
<td>0.021; 0.0005-2; 34200;</td>
<td>+0.55 V</td>
<td>[206]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$-graphene oxide</td>
<td>0.15; 0.001-0.05; -;</td>
<td>+0.60 V</td>
<td>[174]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

According to Table 7, cobalt oxide on pongam seed shells-derived activated carbon possessed the highest sensitivity and the lowest limit of detection of limit.

Incorporation of cobalt oxide on different matrix is not the only method to improve the sensing performance in glucose sensing. Doping cobalt oxides with other materials such as gold [87, 208], zinc oxide [209], PbO$_2$[210], polypyrrole[211], graphene oxide[212], nanoporous carbon synthesized from ZIF-67[204], etc. was explored to improve glucose sensing performance as well. Through multicyclic electrochemical alloying/dealloying method followed by hydrothermal growth of cobalt oxide onto solid nanoporous gold,[208] significantly enhanced glucose sensitivity of 12.5 mA mM$^{-1}$ cm$^{-2}$ was realized with ultra-low limit of detection of 5 nM. Using a combined electrodeposition and galvanic replacement reaction method, flower-like cobalt oxide/Au hierarchical nanostructures modified FTO electrode was prepared and used as enzyme-free system for glucose sensing in alkaline environment.[87] By adopting spin-coating method, layers of Co-oleate and Zn-oleate solution were formed on FTO substrate and calcined to form
Co₃O₄ and ZnO with a ratio of 80:20, which was utilized as catalyst for glucose sensing. A glucose sensitivity of 193 µA mM⁻¹ cm⁻² and the limit of detection of 2 µM in alkaline environment were achieved.[209] The role of ZnO in the binary metal oxide needs further systematic investigation. Other kind of metal oxide, such as PbO₂ was also selected as doping material for Co₃O₄ because of its high electrical conductivity and good stability[210]. In addition, metal-organic framework derived from ZIF-67[213] was used to fabricate nanoporous carbon which was then combined with Co₃O₄ to construct a composite electrode for non-enzymatic glucose sensing and supercapacitor applications.[204] It was worth noting that the as-synthesized MOFs-nanoporous Carbon/Co₃O₄ nanostructure held ultra-low limit of detection of 2 fM and a linear range of 5 fM- 0.205 nM. Table 2 summarized the aforementioned cobalt oxide based non-enzymatic glucose sensors and their sensing performance (the ones presented in Table 1 are not included). It is worth noting that all cobalt oxide based sensors worked in alkaline solution.

Table 8 Comparison of glucose sensing performance of cobalt oxides incorporated sensor

<table>
<thead>
<tr>
<th>Materials</th>
<th>Detection of limit (µM)</th>
<th>Linear Range (mM)</th>
<th>Sensitivity (µA mM⁻¹ cm⁻²)</th>
<th>Applied Potential (V)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co₃O₄-OMC</td>
<td>10</td>
<td>0.01-0.8; 0.9-7</td>
<td>2597.5; 955.9</td>
<td>+0.55</td>
<td>[207]</td>
</tr>
<tr>
<td>Co₃O₄-MPC</td>
<td>5</td>
<td>0.05-0.7; 1.5-6.0</td>
<td>1963.9; 613.4</td>
<td>+0.55</td>
<td></td>
</tr>
<tr>
<td>Co₃O₄-RGO</td>
<td>10</td>
<td>0.1-0.9; 1.0-6.5</td>
<td>1145.2; 506.5</td>
<td>+0.55</td>
<td></td>
</tr>
<tr>
<td>Co₃O₄ nanosheets</td>
<td>0.15</td>
<td>0.001-0.05</td>
<td>-</td>
<td>+0.60</td>
<td>[174]</td>
</tr>
<tr>
<td>Co₃O₄ ultra-nanosheets</td>
<td>1.08</td>
<td>0.005-0.04</td>
<td>1089</td>
<td>+0.35</td>
<td>[214]</td>
</tr>
<tr>
<td>Material/Configuration</td>
<td>Parameter</td>
<td>Value</td>
<td>Unit</td>
<td>Error Margin</td>
<td>Source</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
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<td>--------</td>
</tr>
<tr>
<td>Ni(OH)$_2$/GCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ nanofibers</td>
<td></td>
<td>0.97</td>
<td></td>
<td></td>
<td>[199]</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>36.25</td>
<td></td>
<td>+0.59</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Langmuir isothermal fit</td>
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<tr>
<td>Acicular nanorods</td>
<td></td>
<td>0.058</td>
<td></td>
<td></td>
<td>[201]</td>
</tr>
<tr>
<td>Co$_3$O$_4$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>571.8</td>
<td></td>
<td>+0.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 3.5 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ hollow nanododecahedra</td>
<td>0.58</td>
<td>708.4</td>
<td>+0.55</td>
<td>[203]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.002-0.0606</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionic liquid tagged cobalt-salophen complex</td>
<td>0.79</td>
<td>62 μA/mM</td>
<td>+0.40</td>
<td>[215]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0002-1.8</td>
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</tr>
<tr>
<td>Cobalt phosphide</td>
<td></td>
<td>0.1</td>
<td></td>
<td>+0.60</td>
<td>[216]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0005-1.5 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn doped Co$_3$O$_4$ Film</td>
<td>2</td>
<td>193</td>
<td>+0.52</td>
<td>[209]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.005-0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$/Au</td>
<td></td>
<td>0.1</td>
<td></td>
<td>+0.30; +0.60</td>
<td>[87]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0002-0.2; 0.5-20; 0.002-0.2; 1-20;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6000; 1330;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$-Au Nanowire</td>
<td>0.005</td>
<td>12500</td>
<td>+0.26</td>
<td>[208]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 7; 30-70;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 1.3.2.2.4. Rhodium Oxide & Iridium Oxide Non-enzymatic Glucose Sensor

For the assumption of the oxides from the same group of elements may share similar reactivity toward the same target, rhodium oxide [217] and iridium oxide [218], made from group 9 elements, were fabricated by electrospun-annealing method and then served
as catalysts to oxidize glucose in alkaline aqueous environment. High-temperature annealing enabled iridium oxide nanofibers (IrO2 NFs) were firstly investigated for the catalytic glucose oxidation and it presumably demonstrated the electrocatalytic activity toward glucose attributing to the crystallinity of by high-temperature annealing process. As-prepared sensor can serve as glucose sensor and a solid-state pH sensor. Meanwhile, rhodium oxide formed nanocorals nanostructure and modified on glassy carbon electrode for the first time was reported for the electrochemical glucose oxidation and solid-state pH sensing, reaching a sensitivity of 11.46 µA mM\(^{-1}\) cm\(^{-2}\) and detection of limit of 3.1 µM. It was an interesting strategy to predict the glucose reactivity of rhodium oxide and iridium oxide based on the reports of cobalt oxides[199], made from the same group of element. It provides a good example of predicting metal oxide property and exploring their new sensing application based on the existing study of metal oxide from the same group in period table.

1.3.2.2.2.5. Ferric Oxide Non-enzymatic Glucose Sensor

The research using ferric oxide in non-enzymatic glucose sensing was stimulated by the report of FeOOH nanowires [219] serving as catalyst in enzyme-free glucose sensing system operated in 0.1 M pH7 PBS buffer. The sensing mechanism can be explained by the following reaction scheme:

\[
2\text{Fe(III)} + \text{Glucose} \rightarrow 2\text{Fe (II)} + \text{Gluconolactone} + \text{H}_2\text{O}_2
\]

The presence of ferrous and ferric ions in FeOOH nanowires was ascribed to the key active site in catalytical reaction. Inspired by such idea, ferric oxide was synthesized for non-enzymatic glucose sensing. By mixing FeCl\(_2\) and FeCl\(_3\) with hydroxide ion solution under ultrasonic bath, followed by calcination at 300 °C for 2 h, Fe\(_3\)O\(_4\) nanoparticles were formed and used for catalyst to functionalize multiwalled carbon nanotubes for non-enzymatic glucose sensing in neutral pH.[18] The as-prepared Fe\(_3\)O\(_4\)/MWCNT possessed a high sensitivity of 238.7 µA mM\(^{-1}\) cm\(^{-2}\) and a linear range of 0.5 – 7.0 mM with the limit of detection of 15.0 µM. Furthermore, Naghib et al. [220] reported Fe\(_3\)O\(_4\) with reduced graphene oxide and gelatin for glucose detection at neutral pH with detection limit of 0.024 µM and a linear range of 0.1-10 mM. Fe\(_3\)O\(_4\) was also exploited for glucose
detection in alkaline environment. To facilitate electron transfer and achieve faster diffusion in the sensing area, polypyrrole [221] were employed for the decoration of Fe₃O₄ in glucose detection under an alkaline environment of pH 13.0. A wide linear range of 1-16 mM and a detection limit of 234 µM were reported. However, the high operating pH of this Fe₃O₄ based glucose sensor makes it not as attractive as the ones operated in neutral pH.

1.3.2.2.6. Manganese Oxide Non-enzymatic Glucose Sensor

Even though the low conductivity of MnO₂ film does not favor its sensor application, the coating of gold on MnO₂ nanowires by electrodeposition can significantly improve its glucose sensing performance.[222] Such glucose sensor displayed a sensitivity of 96.30 µA mM⁻¹ cm⁻² (calculated based on the sensitivity of 18.9 µA mM⁻¹ and the use of GCE electrode with a diameter of 5 mm). To improve the conductivity of MnO₂, multiwalled carbon nanotube was also employed to enhance the electrocatalytic ability of MnO₂ toward direct glucose oxidation, which was demonstrated by Chen et al.. [223] The as-prepared sensor possesses a sensitivity of 33.19 µA mM⁻¹ and a linear range up to 28 mM. Since the active area of the modified electrode was not presented in this study, it is difficult to compare its sensitivity performance with other sensors. Unlike aforementioned materials, Wang et al.[224] electrodeposited the electrostatically absorbed Ni²⁺ onto electrodeposited MnO₂ and then applied the composite for glucose detection. A high sensitivity of 1.04 mA mM⁻¹ cm⁻² was achieved in alkaline environment. Other than MnO₂, hierarchical Mn₃O₄ was chronovoltammetrically grown onto nickel foam template followed by etching of nick foam template, thus serving as the catalyst for non-enzymatic glucose sensing.[108] According to the thermogravimetric analysis, there were 44.16% of Mn₃O₄ contained in the composite and the proposed sensor possesses a sensitivity of 360 µA mM⁻¹ cm⁻² toward glucose detection.

1.3.2.2.7. Titanium Oxide Non-enzymatic Glucose Sensor
As a new class of metal oxide, titanium oxide serving as photocatalyst has attracted much more attention in non-enzymatic glucose detection. The following section will convey the key advances of titanium oxide in the application of non-enzymatic glucose sensing.

On the one hand, three-dimensional titanium oxide has been selected as catalyst for direct glucose oxidation [225] because of its high surface to volume ratio. Glucose oxidation was realized because of the conversion between TiO$_2$ and TiOOH at an applied potential of +0.13 V. To further utilize the property of the small band gaps of titanium oxide, Song et al. [129] investigated the effect of 30-min UV light treatment on the performance of sensing materials. The results showed that Pt/Titania nanotube almost recovered to its full response toward 50 mM of glucose after UV light treatment rather than losing its activity toward the same target. As shown in Figure 3, Zhang et al. [226] also developed a glucose sensing system consisting of TiO$_2$-B nanorods and dopamine as well as concanavalin A/BSA for glucose absorbed on SiO$_2$ nanospheres. The glucose detection was operated in 0.1 M pH 6 PBS buffer at an applied potential of -0.2 V with on/off UV light control. The as-prepared glucose sensor possessed an ultra-low limit of detection (50 nM glucose). Most importantly, it opens an avenue in the development of non-enzymatic glucose sensing at neutral pH by simply adapting the unique photocatalytic property of titanium oxide.
1.3.2.2.2.8. Zinc Oxide Non-enzymatic Glucose Sensor

In a similar way, zinc oxide played important role in non-enzymatic glucose detection in two manners that embrace its photocatalytic property and electrochemical catalytic activities.

Zinc oxide was explored as a completely new avenue toward glucose oxidation in neutral pH. Expected by its relative wide band gap, around 3.37 eV[227], zinc oxides possess exceptional optical property. For instance, Hsu et al. [130] reported an enhanced non-enzymatic glucose sensor based on ZnO decorated with Pt nanoparticles. Under UV-light exposure, a sensitivity of 928.1µA mM⁻¹ cm² was achieved. As a comparison, green illumination resulted in a sensitivity of 123.0 µA mM⁻¹ cm². The increased sensitivity of ZnO/Pt sensor under UV light was ascribed to the decreasing of Schottky barrier and the localizing surface plasmonic resonance effect under the illumination environment. Zinc oxide can also mimic enzymatic glucose oxidase to catalyze glucose into hydrogen peroxide and gluconic acid as well.[157, 158] The hydrogen peroxide produced by the proposed reaction was further decomposed to oxygen and water, which was confirmed by the quenching of the light emission intensity as with the increasing of glucose concentration. Figure 4 shows the typical results of photoluminescent (PL) decreased from the increasing of glucose concentration.
In addition, gallium (Ga)-doped ZnO nanorods (GZO NRs) were applied for enzyme free glucose sensing and a sensitivity of 33.4 µA mM⁻¹ cm⁻² was realized[228]. Furthermore, hydrothermally grown zinc oxide was coated with carbon through chemical vapor deposition (CVD),[229] and the as-prepared materials were used for glucose oxidation and showed relatively low sensitivity of 2.97 µA mM⁻¹ cm⁻² compared with Ga-doped ZnO nanorods.

Zinc oxides with different morphologies were also explored for direct glucose oxidation in PBS buffer. The morphology of ZnO was tuned by solvent thermal route with the assistant of amino acids with (or w/o) urea and/or oxalic acid as additives to adjust the pH of the reaction.[230] The optimized starting reagents and additives combinations were selected and three types of ZnO showed good sensitivity toward 10 mM glucose,
including spherical ZCO (made from zinc acetate, cysteine, oxalic acid), nanoparticle ZLU (made from zinc acetate, lysine, urea), and nanosheet ZAU (made from zinc acetate, arginine, urea) with the sensitivity of 64.29 µA mM\(^{-1}\) cm\(^{-2}\), 63.48 µA mM\(^{-1}\) cm\(^{-2}\), and 42.85 µA mM\(^{-1}\) cm\(^{-2}\), respectively. Zinc oxide nanoparticles synthesized using the leaf extract of \textit{Ocimum tenuiflorum} was also applied for the glucose oxidation in alkaline environment with a sensitivity of 631.30 µA mM\(^{-1}\) cm\(^{-2}\) [231].

Therefore, aforementioned metal oxides, titanium oxide and zinc oxide, pave the way of photocatalytic catalysts in both neutral and alkaline pH environment for improved non-enzymatic glucose monitoring.

Table 9 covers the most kinds of composites in terms of the investigation of the metal oxides non-enzymatic glucose performance.

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (µAmM(^{-1})cm(^{-2}))</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ppy-chitosan-Fe(_3)O(_4)/ITO</td>
<td>234 µM</td>
<td>1-16 mM</td>
<td>-</td>
<td>[221]</td>
</tr>
<tr>
<td>rGO/Fe(_3)O(_4)/Gelatin</td>
<td>0.024 µM</td>
<td>0.1-10 mM</td>
<td>-</td>
<td>[220]</td>
</tr>
<tr>
<td>CNT-Fe(_3)O(_4) NPs</td>
<td>15 µM</td>
<td>-</td>
<td>238.7</td>
<td>[18]</td>
</tr>
<tr>
<td>CuO/graphene</td>
<td>1 µM</td>
<td>1 µM-8</td>
<td>1065</td>
<td>[170]</td>
</tr>
<tr>
<td>CuO/rGO</td>
<td>0.1 µM</td>
<td>0.4 µM-12</td>
<td>2221</td>
<td>[168]</td>
</tr>
<tr>
<td>CuOMicro/Nanosheets</td>
<td>20 µM</td>
<td>0.9-16 mM</td>
<td>457.8</td>
<td>[173]</td>
</tr>
<tr>
<td>CuO NPs/Ag/PET</td>
<td>0.3 µM</td>
<td>0.1-15 mM</td>
<td>142.2</td>
<td>[184]</td>
</tr>
<tr>
<td>3D CuONanosheets Cu foil</td>
<td>0.5 µM</td>
<td>0.5 µM-4</td>
<td>4201</td>
<td>[174]</td>
</tr>
<tr>
<td>Cu(_2)O-Shuriken-like</td>
<td>0.035 µM</td>
<td>0.01 µM-11.0 mM</td>
<td>933</td>
<td>[175]</td>
</tr>
<tr>
<td>Cu(_x)O/Ppy/rGO/GCE</td>
<td>0.23 µM</td>
<td>0.1-100</td>
<td>-</td>
<td>[182]</td>
</tr>
<tr>
<td>Material Description</td>
<td>Concentration</td>
<td>Range</td>
<td>Literature</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>CuO NPs-MFI-zeolite-mesoporous/Micro</td>
<td>0.37 µM</td>
<td>0.5 µM-18.4 mM</td>
<td>[232]</td>
<td></td>
</tr>
<tr>
<td>3D-CuO/Graphene-SPE</td>
<td>4 µM</td>
<td>4 µM-13.5 mM</td>
<td>[166]</td>
<td></td>
</tr>
<tr>
<td>ortahedral-Cu$_2$O</td>
<td>128 µM;</td>
<td>300-4100 µM;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QuantumDots/Ortahedral-Cu$_2$O</td>
<td>8.4 µM;</td>
<td>20-4300 µM;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uPod-likeCu$_2$O-(Cu$_2$O-PLNWs/Cu foam)</td>
<td>0.67 µM</td>
<td>1 µM-1.8 mM</td>
<td>[189]</td>
<td></td>
</tr>
<tr>
<td>CuO nanosheets</td>
<td>1 µM</td>
<td>Up to 1 mM;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuO nanoparticles</td>
<td>1 µM</td>
<td>Up to 1.12 mM;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuO nanowires</td>
<td>Up to 1.22 mM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuO/Cu$_2$O nanosheets on Cu foil</td>
<td>0.57 µM</td>
<td>Up to 4 mM;</td>
<td>[178]</td>
<td></td>
</tr>
<tr>
<td>Pd-CuO-galvanic replacement</td>
<td>0.16 µM</td>
<td>0.49 µM-8.0 mM</td>
<td>[118]</td>
<td></td>
</tr>
<tr>
<td>Cu$_x$O(CuO/Cu$_2$O)</td>
<td>0.049 µM</td>
<td>Up to 4 mM;</td>
<td>[233]</td>
<td></td>
</tr>
<tr>
<td>Cu$_2$O/Carbon Vulcan XC-72</td>
<td>2.4 µM</td>
<td>Up to 6 mM;</td>
<td>[171]</td>
<td></td>
</tr>
<tr>
<td>Cu$_x$O NPs-PPyNWs</td>
<td>6.2 µM</td>
<td>Up to 8 mM;</td>
<td>[183]</td>
<td></td>
</tr>
<tr>
<td>Cu$_2$O Nanocubes</td>
<td>3.3 µM</td>
<td>0.3-3.3 mM;</td>
<td>[167]</td>
<td></td>
</tr>
<tr>
<td>Caterpillar-like AuNT Cu$_2$O</td>
<td>1.83 µM</td>
<td>0.1-5 mM;</td>
<td>[179]</td>
<td></td>
</tr>
<tr>
<td>CuO/graphene-SPE-FIA</td>
<td>34.3 nM</td>
<td>0.122 µM-2367</td>
<td>[234]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---------------------------</td>
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<td>-------------</td>
<td>----------</td>
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</tr>
<tr>
<td>CuO Nanocubes-graphene</td>
<td>0.7 µM</td>
<td>0.5 mM</td>
<td>2 µM-4</td>
<td>1360</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mM</td>
<td></td>
</tr>
<tr>
<td>CuO NPs-ink-printed-Au-electrode</td>
<td>0.5 µM</td>
<td>0.1-6.5 mM</td>
<td>2419.8</td>
<td></td>
</tr>
<tr>
<td>CuO-MOF-GCE</td>
<td>70 nM</td>
<td>500 µM-5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mM</td>
<td></td>
</tr>
<tr>
<td>Cu$_2$ONPs-rGO</td>
<td>0.1 µM</td>
<td>0-90 µM;</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100-700 µM</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NP-aggregated CuO</td>
<td>72 nM</td>
<td>Up to 1</td>
<td>2555</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu$_2$O/TiO$_2$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Anodically preparation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-pot-syntheses [237]</td>
<td>1.52 µM</td>
<td>100 µM-3</td>
<td>2682</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanorod-aggregated-flowerlike-CuO-CarbonFiber</td>
<td>0.27 µM</td>
<td>-</td>
<td>6470.6</td>
<td></td>
</tr>
<tr>
<td>3D-rambutan-like-CuO/rGO</td>
<td>0.1 µM</td>
<td>0.5-3.75</td>
<td>52.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuO/TiO$_2$ hollow fiber</td>
<td>0.2 µM</td>
<td>0.2-19.26</td>
<td>1027.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu$_2$O-Cu Foam</td>
<td>5 µM</td>
<td>-</td>
<td>3076</td>
<td></td>
</tr>
<tr>
<td>CuO NW-SWCNT</td>
<td>45.6 nM</td>
<td>1 µM-34</td>
<td>2191.3;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>µM;</td>
<td>761.5;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>34 µM-2.67</td>
<td>mM</td>
<td></td>
</tr>
<tr>
<td>TiO$_2$/CuO</td>
<td>10 µM</td>
<td>10-3600</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>µM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graphene Oxide-CuO NPs</td>
<td>0.69 µM</td>
<td>27.9 µM-</td>
<td>262.52</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>262.52</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Material Description</td>
<td>Concentration Range</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuO NP/inkjet Printed on electrode</td>
<td>0.5 µM 0.05-8.45 mM</td>
<td>[163]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ nanocrystals on carbon matrices</td>
<td>1.0 µM 0.9-7.0 mM</td>
<td>[207]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$-graphene oxide</td>
<td>0.15 µM 1-50 µM</td>
<td>[174]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$-ultra-NSs-</td>
<td>1.08 µM 5-40 µM</td>
<td>[214]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$/Ni(OH)$_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ NF</td>
<td>0.97 µM Langmuir</td>
<td>[199]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ acicular NRs</td>
<td>0.058 µM Up to 3.5 mM</td>
<td>[201]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaf-templated 3D-porous-Co$_3$O$_4$</td>
<td>0.1 µM 1-300 µM</td>
<td>[202]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$Hollow-nanododecahedum</td>
<td>0.24 µM 4-12.5 mM</td>
<td>[389.7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$ NP/GC</td>
<td>0.58 µM 2 µM-6.06 mM</td>
<td>[203]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3D-porous-Co$_3$O$_4$-film-egg-shell-membrane</td>
<td>1.0 µM 0.75-1.5 mM</td>
<td>[205]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zn-doped Co$_3$O$_4$ film</td>
<td>2 µM 5 µM-0.62 mM</td>
<td>[209]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honeycomb-like-porous-Carbon-Co$_3$O$_4$</td>
<td>21 nM 0.05 µM-22 mM</td>
<td>[206]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$/Au</td>
<td>0.1 µM 0.0002-0.2 mM</td>
<td>[87]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5-20 mM; 0.002-0.2 mM; 1-20 mM;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Concentration (Units)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NiO-Au</td>
<td>0.65 μM; 1.32 μM; 0-3 mM; 0-4.5 mM; 23.88; 48.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GO-NiO</td>
<td>0.77 μM 2 μM-0.6 mM; 1100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NiO-mesoporous/Carbon-mesoporous-electrode</td>
<td>0.65 μM 2-1000 μM 834.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NiO NFs—electrospinning-FTO</td>
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<td>1.16 μM Up to 0.5 6302.25</td>
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<td>3D-NiO</td>
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<td>One-step NiO</td>
<td>0.5 μM 2 μM-5.56 376.22</td>
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<td>NPs/polyaniline</td>
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<td>NWs/Graphene oxide/GCE</td>
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<tr>
<td>NiO/NiO-rGO-SPE</td>
<td>1.8 μM 29.9 μM-6.44 mM 1997</td>
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<tr>
<td>Nitrogen-doped-Carbon NF</td>
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<tr>
<td>NiOx</td>
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<td></td>
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<tr>
<td>IrO$_2$@NiO core-shell structure</td>
<td>0.31 μM 0.5 μM-2. 1439.4</td>
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<tr>
<td>ZnO NWs/Pt</td>
<td>- Up to 15 928.1; 123.0</td>
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<tr>
<td>3D-graphene/Ni-on-ZnO nanorod arrays</td>
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<tr>
<td>ZnO NPs</td>
<td>0.043 μM 1-8.6 mM 631.3</td>
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<td>ZnO nanostructures</td>
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<td>ZnO nanorod</td>
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<tr>
<td>Ga-doped ZnO nanorods</td>
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<tr>
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<td>0.3 μM 5 μM-1.1 609.8</td>
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References: [61, 103, 110, 116, 120, 124, 128, 130, 131, 135, 138, 140, 144, 149, 151, 155, 158, 162, 165, 170, 174, 178, 182, 186, 190, 193, 195, 196, 197, 198, 203, 205, 210, 215, 220, 225, 230, 231]
<table>
<thead>
<tr>
<th>Material</th>
<th>Concentration (mM)</th>
<th>Sensitivity (µA cm⁻²)</th>
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<tr>
<td>doped-SnO₂</td>
<td>0.1-10</td>
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<tr>
<td>Carbon-coated-ZnO</td>
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<td>20-190</td>
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<tr>
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<tr>
<td>TiO₂ NT-Pt NPs</td>
<td>0-</td>
<td>-</td>
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<tr>
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<td>24 µM</td>
<td>3690</td>
</tr>
<tr>
<td>TiO₂-B</td>
<td>50 nM</td>
<td>-</td>
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<tr>
<td>photoelectrochemical sensing</td>
<td></td>
<td></td>
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<tr>
<td>Ppy-Chitosan-TiO₂</td>
<td>614 µM</td>
<td>-</td>
</tr>
<tr>
<td>Ni/NiTiO₃/TiO₂</td>
<td>0.7 µM</td>
<td>456.4</td>
</tr>
<tr>
<td>Mn₃O₄/3D grapheme foam</td>
<td>10 µM</td>
<td>360</td>
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<tr>
<td>Phage-templated MnO₂</td>
<td>1.8 µM</td>
<td>-</td>
</tr>
<tr>
<td>NWs M13-E4@ MnO₂ (Enzymatic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tin Oxides (SnO₂)–Au-film</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pt/Cu₂S/SnO₂</td>
<td>-</td>
<td>280</td>
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</tbody>
</table>

From the periodic table, one can find that copper based oxides nanostructure are the most extensively studied, however, that in group 9, including cobalt, rhodium, iridium, etc, its oxides have unique performance towards enzyme-free glucose detection. Cobalt oxide has been reported with outstanding performance for direct glucose oxidation with good sensitivity and selectivity[199, 201] due to its isoelectric point smaller than the electrolyte that used for glucose detection, resulting in negative charged surface. Thus it leads to the good selectivity. In the same group, iridium oxide has been decorated with nickel oxide as core-shell structure[151] with 1439.4 µA mM⁻¹ cm⁻² sensitivity and good selectivity. The core-shell structure intrinsically provides more electrons to the active site, NiO, due to larger electronegativity of NiO compared with IrO₂. Thus the sensitivity
of such core-shell structure improved the sensitivity compared with no iridium oxide combined with.

Group 9 is brought into attentions as the major research materials in the following sections in terms of its dual functional sensing and this will be discussed in Chapter 2, 3, 4, and 5.

1.4 Motivation, Objectives and Organization

1.4.1 Motivation

Although both solid-state pH sensors and metal oxide based non-enzymatic glucose sensors have been extensively and individually studied, it still remains unmet challenge to develop a single sensing material for both non-enzymatic glucose and solid-state pH sensing. This is mainly attributed to the lack of both pH-sensitive and glucose-responsive sensing materials. Therefore, new functional materials or existing materials with new functionality should be developed and/or identified in order to accomplish aforementioned dual sensor concept.

1.4.2 Objectives

This Ph.D. project aims to investigate dual functional metal oxides nanomaterials for both glucose detection and pH sensing, mainly focus on the metal oxides from group 9 elements, with good selectivity, sensitivity, potential clinical application such as human serum sample tests, to broad the scope of metal oxides materials for the sensing of glucose with intact pH sensing property.

1.4.3 Organization

The dissertation is divided into 5 chapters apart from the Introduction (Chapter 1). Based upon the hypothesis of this Ph.D. project, the metal oxides from group 9 elements should possess dual functions both in glucose oxidation sensing and pH sensing. Chapter
2 discussed about the synthesis of iridium oxide nanofibers, morphological and surface characterization of as-prepared iridium oxides, the details of sensitivity and selectivity as well as the human serum sample testing were systematically investigated in this chapter. In addition, pH titration experiments and sensing performance were revealed. Chapter 3 followed such experiment design with rhodium oxide nanocorals as moiety for dual functional nanomaterials studies. The rhodium oxides were also electrospun and annealed for the modification on glassy carbon electrode for both direct glucose oxidation and pH sensing explorations. Afterwards, pH-sensing property was carefully investigated in the end.

With cobalt oxides, we revisited such materials by using coaxial electrospinning-annealing process to fabricate core-shell structure nanofibers of cobalt oxides in Chapter 4. The as-prepared core-shell cobalt oxides were systematically investigated both in morphological and surface characters by transmission electron microscopy, scanning electron microscopy, Raman spectroscopy, X-ray photoelectron microscopy, etc., and the electrochemical characterizations were further studied as well as its pH sensing performance.

Last but not least, Au-doped iridium oxide nanoclusters were fabricated through electrospinning-annealing two-step process for the modification of glassy carbon electrode for the non-enzymatic glucose and solid-state pH sensing for decreased operational potential in amperometry electrochemical test in Chapter 5.

As a summary, chapter 6 gives a general conclusion of the designed experiments and results as well as some future opportunities in such field of area.
Chapter 2

High-temperature Annealing Enabled Iridium Oxide Nanofibers for both Non-enzymatic Glucose and Solid-state pH Sensing
Abstract
As a new class of multifunctional material, high-temperature annealing enabled iridium oxide nanofibers (IrO$_2$ NFs) were synthesized and then employed as the sensing element to fabricate a novel dual glucose and pH sensor in this study. The as-prepared IrO$_2$ NFs were systematically characterized using scanning electron microscopy, X-ray diffraction, X-ray photoelectron spectroscopy, and Raman spectroscopy, while the electrochemical and electrocatalytic performance of the IrO$_2$ NFs based dual sensor toward pH and glucose sensing were evaluated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively. The IrO$_2$ NFs not only possess good and reversible pH sensitivity as expected, but also demonstrate the electrocatalytic activity toward glucose which was presumably attributed to the crystallinity enabled by high-temperature annealing effect during the preparation of IrO$_2$ NFs. This unique dual functionality enables us to develop a sensor which can be applied for both non-enzymatic glucose and solid-state pH sensing. The experiment results show that the IrO$_2$ NFs based dual sensor exhibits a Nernst constant close to a theoretical value with excellent reversibility in pH titration, while it also possesses a sensitivity of 22.22 $\mu$A·mM·cm$^{-2}$, a limit of detection of 2.9 $\mu$M (S/N=3), and good selectivity against various interferents in non-enzymatic glucose detection. Its good accuracy for detecting glucose in human serum sample was also demonstrated by comparing to commercial glucose meter. All these features indicate that the high-temperature annealed IrO$_2$ NF is a promising multifunctional sensing material in the development of an integrated solid-state pH sensor and non-enzymatic glucose sensor.

Keywords: iridium oxide; nanofibers; electrospinning; non-enzymatic; glucose detection; pH sensing; dual sensor
2.1 Introduction
As two very important sensors, pH sensor and glucose sensor have been individually investigated and widely used in the past decades. On one hand, pH sensor is a routine instrument used in research laboratories and various industrial sectors to probe the acidity or alkalinity of aqueous solutions. Up to date, the most widely used pH sensor is conventional glass-type electrode which typically suffers from the disadvantage of the brittleness. Ion-sensitive field-effect transistor and optical pH sensors are thus developed with improved durability, however, they have power consumption concern and are not suitable for some specific applications. Therefore, solid-state pH sensor, which shares the similar detecting principle (electromotive force between sensing and reference electrodes) as conventional glass-type pH sensor, gradually becomes the trends in the development of pH sensor due to its durability, low cost and small size. In this regard, various solid-state metal oxides (e.g., IrO$_x$[248], RhO$_2$[249], SnO$_2$[250, 251] RuO$_2$[252, 253], etc.) have been exploited as potential sensing materials of solid-state pH sensor. On the other hand, glucose detection is of paramount importance for patients with diabetes. Currently enzyme-based glucose sensors dominate the market for blood glucose monitoring. However, the intrinsic instability of enzyme could limit the shelf life of the glucose sensing strips. Therefore, non-enzymatic glucose sensors are developed as an alternative. Among all types of non-enzymatic glucose sensors, metal oxides based electrochemical glucose sensors show promising due to their economic advantage and chemical/thermal stability. Up to date, various metal oxides and their composites (e.g., Co$_3$O$_4$[87, 174, 199, 201-203, 205-207, 209, 214, 242], Co$_3$O$_4$/graphene[254], TiO$_2$ modified Co$_3$O$_4$[255], NiO[150, 151, 193, 195, 196, 198, 243], noble metal doped NiO[155, 156, 256], CuO[163, 165, 166, 168, 170, 172-174, 177, 180, 181, 184, 185, 232, 234, 236, 238, 239, 241, 257], Cu$_2$O[167, 169, 171, 175, 179, 189, 232, 240], mixture of CuO and Cu$_2$O[178], CuO-Pd[118], CuO-TiO$_2$[187-189], CuO-CNT[164], Cu$_x$O[182, 183], NiO/CdO[258], etc.) have been explored regarding its glucose oxidation sensing performance.

Although both solid-state pH sensing and metal oxide based non-enzymatic glucose sensing topics have been extensively and individually studied, the pursuit of single sensing material for both non-enzymatic glucose and solid-state pH sensing still remains
unmet challenge due to the lack of multifunctional sensing materials. Therefore, new functional materials or existing material with new functions should be developed and/or identified in order to accomplish aforementioned dual sensor concept.

In the same group, elements share similar behavior. With such kind of consciousness, should one focus on the group 9, which includes cobalt (Co), rhodium (Rh), iridium (Ir), and meitnerium (Mt), it would bring some spotlight for the predictable trend of their corresponding oxides toward glucose and pH monitoring. In our previous studies[259], iridium oxide has been applied in the development of solid-state pH sensor, while cobalt oxide (Co3O4) nanofibers was reported for non-enzymatic glucose detection[199]. According the hypothesis that the oxides from the same group elements share similar behavior, one can expect that iridium oxide should possess dual function towards both pH and glucose sensing. However, the application of iridium oxide as a dual functional material to fabricate a dual sensor for pH and glucose detection is rare as the commercially available iridium oxide only shows pH sensitivity but lack of electrochemical catalytic activity toward glucose in alkaline environment (Figure S1A).

A recent paper by Wang et al.[151] reports the use of electrospun IrO2 nanofibers as the template to synthesize IrO2/NiO core-shell structure, which was further employed for non-enzymatic glucose detection. However, NiO was claimed to be the active site for glucose oxidation and responsible for the signal, while iridium oxide only played the role of the supporting core for the growth of glucose catalyst NiO.

Therefore, this study aims to develop a dual electrochemical sensor for both glucose and pH sensing using single sensing material. IrO2 nanofibers (IrO2 NFs) were prepared by electrospinning followed by high temperature treatment. It was found that high temperature treatment endows prominent glucose oxidation activity to the as-prepared IrO2 NFs without sacrificing its pH sensitivity, thus offering a unique sensing material in the development of a dual sensor for both glucose and pH sensing.

2.2 Experimental Section

2.2.1. Materials

Iridium (IV) tetrachloride was purchased from Alfa Aesar and used without further purification. Polyvinylpyrrolidone (PVP, MW=1,300,000) and Nafion 117 solution
(purum, ~20% in a mixture of lower aliphatic alcohols and water) were supplied from Sigma-Aldrich. Dimethylformamide (DMF), D-(-)-glucose, 4-acetaminophen, ascorbic acid, and uric acid, as well as ethanol were obtained from Acros Organics. 10 mM pH 7.4 PBS buffer contained 137 mM NaCl, 2.7 mM KCl, 10 mM Na$_2$HPO$_4$, and 1.8 mM KH$_2$PO$_4$. All aqueous solutions were prepared with deionized water (18.2 MΩ-cm) generated by a Barnstead water system.

2.2.2 Preparation of Iridium Oxide (IrO$_2$) Nano-fibers

0.19 g Iridium tetrachloride was dissolved in 4 mL of DMF solution, followed by the addition of 0.87 g PVP. The mixed solution was under magnetic stirring for overnight. The as-prepared homogenous solution was then electrospun using 23-gauge needle with a flow rate of 0.3 mL/h at an applied voltage of 20 kV over an aluminum foil collector of 15 cm distance. The IrCl$_4$/PVP nanofibers collected on the collector were then peeled off. After 3 hours pre-dry step at 80 °C in an oven, the as-prepared precursory IrCl$_4$/PVP nanofibers were calcined under air atmosphere at 900 °C for 3 hours with a ramp-up speed at 2 °C/min. The furnace was then allowed to naturally cool down to room temperature and the annealed IrO$_2$ NFs were collected.

2.2.3 Preparation of IrO$_2$ NFs Modified Glassy Carbon Electrode and Screen-printed Electrode

Before surface modification, glassy carbon electrode (GCE, dia. 3 mm) was polished with 1 μm and 0.05 μm alumina slurries sequentially, and then rinsed with DI water. Finally, the electrode was sonicated in ethanol and deionized water, dried at room temperature, and ready for modification. To prepare 5 mg/mL IrO$_2$ NFs suspension, 5 mg of calcined IrO$_2$ sample was suspended in 1.0 mL ethanol and then subject to 30 minutes of ultra-sonication. Finally, 6 μL IrO$_2$ NFs/ethanol suspension was drop-cast onto pre-cleaned glassy carbon electrodes. After solvent evaporation, the same volume of Nafion solution (1 wt% in ethanol) was further cast onto the top of IrO$_2$ NFs and dried in air to entrap the nanofibers. The as-prepared electrode is denoted as IrO$_2$ NFs-Nafion/GCE. Nafion-coated glassy carbon electrodes (Nafion/GCE) were also prepared as the control electrode following the same procedure. Before use, each electrode was submerged into
DI water for 1 h to allow Nafion membrane to swell. All experiments were repeated at least 3 times to ensure the reproducibility.

To achieve one step closer to real product configuration, screen-printed electrodes (SPE, a gift from GSI Technologies Co.) consisting of two carbon planar electrodes as working and counter electrodes and a solid-state silver-silver chloride (Ag-AgCl) reference electrodes were employed. The screen-printed working electrode was modified with a layer of IrO₂ NFs followed by another layer of Nafion, following a similar procedure as described above but with the use of a smaller volume (3 µL) in order to avoid the overspreading of IrO₂ NFs suspension to counter and reference electrodes printed on the same strip. The as-prepared SPEs were also investigated for pH and glucose sensing.

2.3 Results and Discussion

2.3.1 Morphology and Composition of IrO₂ NFs

Various iridium oxide nanomaterials have been prepared using IrCl₃ as the precursor and then used as the supporting template to further grow single crystalline RuO₂ [260] and NiO[151]. In this study, we first used iridium tetrachloride mixed with PVP in DMF solution for electrospinning, thus fabricating the precursory nanofibers. The presence of PVP could improve the viscosity of the mixture, thus favoring the electrospinning of nanofibers. High-temperature calcination of the precursory nanofibers thus removed the matrix polymer and generate IrO₂ nanofibers. Figure 2.1A showed the typical morphology of the precursory IrCl₄/PVP nanofibers, while Figure 2.1B displayed the morphology of IrO₂ nanofibers after annealing process at 900 °C for 3 hours. One can see that the precursory nanofibers possessed smooth surface and the nanofiber morphology was generally maintained after the degradation of PVP and decomposition of IrCl₄ after high temperature treatment. However, the diameters of the nanofibers decreased from 132.89 ± 39.20 nm (IrCl₄/PVP nanofibers) to 44.80 ± 16.23 nm (IrO₂ nanofibers), which could be attributed to the loss in total mass upon calcination. In addition, the high-temperature annealed IrO₂ nanofibers were composed of numerous nanoparticles with relatively uniform distribution and their surfaces are not smooth any more (Figure 6B), which could provide numerous accessible surface area for the subsequent electrochemical sensing.
Figure 2.1 Typical SEM images of IrCl$_4$/PVP nanofibers (A) and IrO$_2$ nanofibers after calcination at 900 °C for 3 hours (B). Inset: higher magnification of IrCl$_4$/PVP nanofibers and IrO$_2$ nanofibers. Scale bar is 1 µm in A and B and 100 nm in Inset, respectively.

To further investigate the crystal structure and phase purity of iridium oxide nanowires, X-ray diffraction was carried on and the result was showed in Figure 2.2. The reflections at $2\theta=27.85^\circ$, 34.51°, 39.80°, 40.44°, 53.79°, 57.77°, 58.21°, 65.39°, 65.91°, 69.06°, 73.14° were detected in the as-prepared IrO$_2$ NFs. Except one very minor peak at $2\theta=47.12^\circ$, all other peaks fit well with IrO$_2$ (110), (101), (200), (111), (211), (220), (002), (310), (112), (301), (202) (JCPDS Card File No. 15-0870), which indicate the typical cubic fluorite-like structure of IrO$_2$. A minor impurity peak labeled by star symbol of $2\theta=47.12^\circ$ may be attributed to the residual of iridium tetrachloride which is not fully calcinated. Typical Raman spectra of the as-prepared IrO$_2$ NFs sample and the precursory IrCl$_4$/PVP nanofibers are shown in Figure 2.3. There is no obvious peak observed for precursory nanofibers. However, there are three major peaks at 554, 725 and 738 cm$^{-1}$ for the sample after high-temperature treatment of precursory nanofibers. Those peaks can be assigned to E$_g$, B$_{2g}$ and A$_{1g}$ modes of the crystalline IrO$_2$, further indicating the formation of IrO$_2$ [261].
Figure 2.2 XRD pattern for the calcined IrO$_2$ nanofibers.

Figure 2.3 Raman spectra of IrCl$_4$/PVP nanofibers (red line) and IrO$_2$ nanofibers (black line), respectively.

Not enough by XRD to probe the surface elements and groups, XPS spectroscopy was employed to investigate IrO$_2$ NFs atomic orbital structure. The binding energies were calibrated based on the C 1s line at 284.8 eV and Shirley background subtraction was
applied to the raw data before deconvolution. Figure 2.4A shows the XPS survey spectrum for IrO$_2$ NFs, indicating that the as-prepared IrO$_2$ NFs are mainly composed of iridium and oxygen (carbon peak is attributed to the carbon tape used). The high resolution of spectra of Ir4f and O1s are presented in Figure 2.4B and 2.4C, respectively. In Figure 2.4B, O1s shows the core-level doublet peaks and can be de-convoluted into 3 peaks by using Gaussian curve fitting. The accurate peak positions were determined to be 529.29 eV, 530.95 eV and 532.38 eV. Specifically, the de-convoluted peak of 529.29 eV of O1s is in good agreement with reported energy of vertically aligned IrO$_2$[262, 263]. The Ir4f signal of nanofibers illustrates that the iridium atoms have two different binding states. The peaks identified as [Ir$^{4+}$]4f$^7$/2 and 4f$^5$/2 at 61.15 and 64.30 eV, respectively. They are attributed to the 4+ oxidation state of iridium, and have the similar value compared with single crystal IrO$_2$, which have values of 61.7 and 64.7 eV, respectively[262]. Quantitative analysis of the peak areas indicates the surface of the nanofibers is highly oxygen-enriched surface. In conclusion, as-prepared iridium oxide has the +4 valence on the analyzed surface of IrO$_2$ NFs powder.
Figure 2.4 (A) The survey spectrum for IrO2 nanofibers; (B) and (C) The high resolution of spectra for O1s and Ir4f regions of IrO2 nanofibers, respectively.
2.3.2 Electrochemical behavior of the IrO$_2$ NFs modified GCE (IrO$_2$ NFs-Nafion/GCE) toward glucose and pH monitoring

2.3.2.1 Glucose sensing

Iridium has been reported to form complex with different oxidation valences[264, 265], which endow the electrochemical oxidation/reduction feasible. The CVs of the Nafion/GCE (Figure 2.5A, traces a and b) and IrO$_2$ NFs-Nafion/GCE (Figure 2.5A, traces c and d) in the presence and absence of 5 mM glucose were first investigated in alkaline solution (0.1 M NaOH), ranging from 0 V to 0.8 V vs. Ag/AgCl. The corresponding results are presented in Figure 2.5A. In the absence of glucose, there is no obvious peak observed on the Nafion/GCE, while there is a pair of well-defined quasi-reversible redox peaks on IrO$_2$ NFs-Nafion/GCE with the anodic peak potential at ca. +0.68 V and the cathodic peak at ca. +0.64 V. According to the difference between the anodic peak potential and the cathodic peak potential equals to 2.2RT/nF [266] the calculated value for n (1.88) is close to 2, indicating that 2-electron transfer might involve in this redox reaction ($\text{Ir}^{4+}/\text{Ir}^{6+}$) in basic condition. Two-electron-transfer of electrodeposited IrOx film was also observed in basic medium[267], which is consistent with our results. Upon the addition of 5 mM glucose, there is no obvious glucose oxidation observed on the Nafion/GCE, while the anodic peak current significantly increased on the IrO$_2$ NFs-Nafion/GCE due to the glucose oxidation on IrO$_2$ NFs to generate gluconolactone. There are a large number of reports about non-enzymatic glucose sensing in alkaline solution using various metal or metal oxides, including Cu[268], Pt-Au[71], NiO-Au [156], NiO-CdO[258] Co$_3$O$_4$[124, 201, 254, 255], Co$_3$O$_4$/graphene[254], Co$_3$O$_4$/CeO$_2$[269], MnO$_2$/MWCNT[270], Cu/MnO$_2$[271] Ir$_{0.3}$Mn$_{0.7}$O$_2$[272] etc. However, the glucose oxidation on IrO$_2$ is barely studied as IrO$_2$ is mostly used as the supporting template to grow NiO (IrO$_2$@NiO core-sheath structure)[151] in which NiO is responsible for glucose sensing. According the mechanism proposed in the literature based on various metal oxides and the fact of two-electron transfer process for IrO$_2$ oxidation, the glucose oxidation on IrO$_2$ NFs in alkaline solution can be presumably expressed as following reactions:

$$\text{IrO}_2 + 2\text{OH}^− \rightarrow \text{IrO}_2(\text{OH})_2 + 2\text{e}^− \quad (1)$$
$(\text{IrO}_2\text{(OH)})_2 + \text{glucose} \rightarrow \text{IrO}_2 + \text{gluconolactone} + 2\text{H}_2\text{O} \quad (2)$

When the same IrO$_2$ NFs-Nafion/GCE was run in neutral PBS buffer in the absence and presence of 5 mM glucose, there is no obvious peak observed in both cases, indicating the requirement of OH$^-$ in glucose oxidation on IrO$_2$ NFs.

Figure 2.5 (A) CVs of the Nafion/GCE (a and b) and IrO$_2$ NFs-Nafion/GCE (c and d) in 0.1 M NaOH in the absence (a and c) and presence (b and d) of 5 mM glucose, respectively. (B) CVs of the IrO$_2$ NFs-Nafion/GCE in 0.1 M pH 7.4 PBS buffer solution (e and f) and 0.1 M NaOH solution (g and h) in the absence (e and g) and presence (f and h) of 5 mM glucose, respectively. (C) CVs of the IrO$_2$ NFs-Nafion/GCE in 0.1 M solution at various scan rage of 10, 20, 40, 60, 80, 100, 150, 200 mV/s. (D) Plot of peak current vs. square root of scan rate.
In our previous study, commercial iridium oxide powder from Sigma has been employed to develop solid-state pH sensor[259]. However, the GCE electrode modified with commercial iridium oxide powder did not possess glucose oxidation capability (Figure 2.6A) and also there is no amperometric signal upon glucose addition at an applied potential of +0.68 V (data not shown). To understand the origin of glucose oxidation capability in the high-temperature annealed IrO$_2$ NFs, the commercial iridium oxide powder was calcined at 900 °C for 3 hours. As shown in Figure 2.7, commercial iridium oxide is amorphous (no obvious peak in XRD study), but the calcined commercial iridium oxide sample displays good crystallinity and shows similar XRD pattern as that of the as-prepared IrO$_2$ NFs. More interestingly, the calcined commercial iridium oxide modified GCE possesses good glucose oxidation capability (Figure 2.6B and 2.6C), indicating that during calcination of precursory nanofibers, high-temperature annealing enabled the good crystallinity in IrO$_2$ NFs. Such good crystallinity can be attributed to the observed glucose response.

![Figure 2.6](image_url)

**Figure 2.6.** (A) CVs of commercial iridium(IV) oxide powder modified glassy carbon electrode in 0.1 M NaOH solution with various glucose concentrations; (B) CVs of high-temperature annealed commercial iridium(IV) oxide powder modified glassy-carbon electrode in 0.1 M NaOH solution with various glucose concentrations; (C) Amperometric response of high-temperature annealed commercial iridium(IV) oxide powder modified screen-printed electrode with successive additions of 0.5 mM, 1.0 mM, 2.0 mM, 5.0 mM, and 10.0 mM glucose into 0.1 M NaOH at an applied potential of +0.68V.
Figure 2.7. XRD patterns of commercial iridium (IV) oxide powder (black line) and annealed commercial iridium (IV) oxide powder after calcination at 900 °C for 3 hours.

Furthermore, the effect of scan rates on the oxidation and reduction peak currents were studied and the corresponding result was presented in Figure 2.5 C and 2.5D. One can see that the redox peak currents increased linearly with the scan rate in the range from 10 mV/s to 200 mV/s (Figure 2.5D), indicating a surface-controlled electrochemical process. As the scan rate varied, however, the anodic peak position and cathodic peak position did not shift, indicating that iridium oxide involved in a quasi-reversible reaction.
Figure 2.8 (A) Amperometric response of the IrO$_2$ NFs-Nafion/GCE with successive additions of 100 µM glucose into 0.1 M NaOH at an applied potential of +0.68 V. Inset: the comparison of the amperometric responses from IrO$_2$ NFs-Nafion/GCE and the Nafion/GCE (control). (B) The corresponding calibration curve with fitting curve. Error bars indicate the standard deviation for triplicate measurements.

As the oxidation (anodic) peak current at ca. +0.68 V increases proportionally with glucose concentration, amperometric detection of glucose using IrO$_2$ NFs-Nafion/GCE was conducted at an applied potential of +0.68 V (vs. Ag/AgCl). Figure 2.8A shows the typical amperometric responses of the developed sensor to successive injection of glucose in 0.1 M NaOH solution. There is no glucose oxidation observed on the control electrode (Nafion/GCE). On the contrary, a well-defined, stable and fast amperometric response within 5 s can be observed on the IrO$_2$ NFs-Nafion/GCE. With the successive addition of glucose, the IrO$_2$ NFs-Nafion/GCE yields a stepwise amperometric response. The amperometric current increased proportionally with the increase of glucose concentration at the IrO$_2$ NFs-Nafion/GCE. The corresponding calibration plot of the current vs. glucose concentration was shown in Figure 2.8B. The electrochemical oxidation of glucose on IrO$_2$ NFs is a surface catalytic reaction, which is typically well-described by Langmuir isothermal theory in our previous study[199]. Therefore, Langmuir isothermal theory was employed to fit the calibration curve (Figure 2.8B). Concentration of glucose absorbed on the catalyst surface ($C_{glucose_s}$) can be expressed as:
where \( C_{glucose} \) is the glucose concentration in solution, \( C_t \) is a constant reflecting the total molar concentration of active sites on IrO\(_2\) NFs, and \( K_A \) is the adsorption equilibrium constant. At a fixed applied potential in amperometric detection, the current response \( I \) resulted from the glucose electrochemical oxidation on the surface of IrO\(_2\) NFs can be considered as an element reaction with a rate constant of \( K_B \), thus being proportional to \( C_{glucose} \). Therefore, one can derive following equation to correlate \( I \) with \( C_{glucose} \).

\[
I = K_B C_{glucose} = \frac{K C_{glucose}}{1 + K_A C_{glucose}} \quad (K = K_A K_B C_t)
\]

The experimental data was used to fit the equation above and the solid curve in Figure 2.8B represents the corresponding fitting curve. One can see that the calibration data fit into this equation very well with \( K=1.570 \) and \( K_A=0.133 \) (a correlation coefficient of 0.999), thus \( I \) can be expressed as follows:

\[
I = \frac{1.570 C_{glucose}}{1 + 0.133 C_{glucose}}
\]

At low glucose concentration (i.e. \( 0.133 C_{glucose} \ll 1 \)), the equation above can be derived as \( I = 1.570 C_{glucose} \). According to the surface area of GCE, the sensitivity and the limit of detection (S/N=3) are calculated to be \( 22.22 \mu A \text{mM}^{-1} \text{cm}^{-2} \) and 2.93 \( \mu \text{M} \), respectively. The sensitivity and the limit of detection are comparable to most of other non-enzymatic glucose sensors (Table 2.1).

**Table 2.1. Comparison of various non-enzymatic glucose sensors**

<table>
<thead>
<tr>
<th>Sensing Materials</th>
<th>pH</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity/( \mu A \text{mM}^{-1} \text{cm}^{-2} )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt-Au</td>
<td>7 and 13</td>
<td>3.2 ( \mu \text{M} )</td>
<td>0-22 mM</td>
<td>24.6</td>
<td>[71]</td>
</tr>
<tr>
<td>NiO-CdO</td>
<td>13</td>
<td>0.35 ( \mu \text{M} )</td>
<td>0-6.37 mM</td>
<td>212.71</td>
<td>[258]</td>
</tr>
<tr>
<td>Material</td>
<td>Concentration</td>
<td>Method</td>
<td>Sensitivity</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Co$_3$O$_4$</td>
<td>0.97 µM</td>
<td>Langmuir-Isothermal fit</td>
<td>36.25</td>
<td>[199]</td>
<td></td>
</tr>
<tr>
<td>NiO-Au</td>
<td>1.32 µM</td>
<td>Up to 3 mM</td>
<td>48.35</td>
<td>[156]</td>
<td></td>
</tr>
<tr>
<td>MnO$_2$/MWNT</td>
<td>1 mM</td>
<td>0-28 mM</td>
<td>33.19</td>
<td>[270]</td>
<td></td>
</tr>
<tr>
<td>IrO$_2$@NiO</td>
<td>0.31 µM</td>
<td>0.5 µM-2.5 mM</td>
<td>1439.4</td>
<td>[151]</td>
<td></td>
</tr>
<tr>
<td>PtM (M=Ru,Pd and Au)</td>
<td>neutral</td>
<td>Up to 15 mM</td>
<td>10.7</td>
<td>[273]</td>
<td></td>
</tr>
<tr>
<td>PdNPs-FCNTs</td>
<td>-</td>
<td>0-46 mM</td>
<td>11.4</td>
<td>[112]</td>
<td></td>
</tr>
<tr>
<td>Ga-doped ZnO nanorods</td>
<td>-</td>
<td>Up to 10 mM</td>
<td>33.4</td>
<td>[274]</td>
<td></td>
</tr>
<tr>
<td>IrO$_2$ NFs</td>
<td>2.9 µM</td>
<td>Langmuir-Isothermal fit</td>
<td>22.22</td>
<td>This work</td>
<td></td>
</tr>
</tbody>
</table>

The selectivity of the IrO$_2$ NFs-Nafion/GCE was also investigated against normally co-existed interfering species with glucose such as dopamine (DA), ascorbic acid (AA), 4-acetoamenophen (4-AP) and uric acid (UA). As the concentration of glucose in blood is typically at least 10-fold higher than those of common interferences, the amperometric signal of 100 µM glucose on the IrO$_2$ NFs-Nafion/GCE was compared with those of 10 µM 4-AP, UA, AA, and DA. Similar selectivity study was also reported by Wang, J. et al. [151]. Figure 2.9A showed the current vs time curve of the IrO$_2$ NFs-modified electrode toward the sequential injection of glucose and interfering species. Except that DA results in a minor response, the interference from 4-AP, UA and AA was negligible, indicating good selectivity of the developed non-enzymatic glucose sensor.

As an example of a practical use, the detection of glucose in humans serum sample was also conducted using the as-developed glucose sensor and the measured result was
compared to that from commercial glucose meter (OneTouch UltraMini, LifeScan, Inc, CA). As shown in Figure 14B, the measured glucose concentration (6.15 mM) by our non-enzymatic glucose sensor is in good agreement with the value (6.00 mM) measured using the commercial enzyme-based glucose sensor, indicating the accuracy of the developed sensor. In addition, the low relative standard deviation shown in Figure 2.9 suggests the good reproducibility of the developed non-enzymatic glucose sensor.

![Figure 2.9](image)

**Figure 2.9 (A)** Amperometric response curve of the IrO$_2$ NFs-Nafion/GCE to the addition of 100 µM glucose, 10 µM DA, 100 µM glucose, 10 µM 4-AP, 100 µM glucose, 10 µM AA, 100 µM glucose, 10 µM UA in 0.1 M NaOH solution at an applied potential of +0.68V. **(B)** Glucose concentration in human serum sample determined by commercial glucose meter (One Touch UltraMini, LifeScan) and the developed sensor in this study.

### 2.3.2.2. pH sensing

Iridium oxide has well-documented and robust electromotive force (EMF) variation with local pH change in aqueous condition[275, 276]. Since Yamanka et al. [277] firstly reported the anodically oxidized iridium oxide (AOIRF) and cathodically oxidized iridium oxide (COIRF), iridium oxide has been extensively exploited for solid-state pH detection. The pH sensing mechanism of iridium oxide has being well-investigated, which typically involves in pH-dependent redox intercalation equilibrium among different oxidation states of IrO$_x$. To further demonstrate the as-developed IrO$_2$ NFs-Nafion/GCE as a solid-state pH sensor, pH titration was conducted from pH 3 to pH 9 and then back to
pH 3 as well as from pH 9 to pH 12 and then back to pH 9. The corresponding EMF value was recorded in real-time format and shown in Figure 2.10 A and 2.10D. The actual pH value in solution was measured using a commercial pH meter. One can see that the sensor responded to pH variation rapidly and the relative stable potential were typically obtained within 8 seconds, which is better than the stabilizing time for commercial pH meter. The calculated Nernst constants are 62.32 mV/pH (titration from pH 3 to pH 9), 65.05 mV/pH (titration from pH 9 to pH 3), 55.93 mV/pH (titration from pH 9 to pH 12) and 62.98 mV/pH (titration from pH 12 to pH 9). Such observed hysteresis, which is represented by the difference of the electrochemical potentials at the same pH level, can be attributed to a number of factors such as slightly different thermodynamic equilibrium established at the same pH during titration, which may result from different oxidation states, the nanostructures, and/or the hydration degree on the IrO$_2$ NFs. Although slightly different, they are in agreement with the theoretical value of 59 mV at room temperature. This study further corroborates the claim that the developed IrO$_2$ NFs modified sensor can be applied for both glucose and pH detection.

Figure 2.10 Electromotive force (EMF) vs. time curves for IrO$_2$ NFs-Nafion/GCE during reversible and repeatable pH titration cycles and their corresponding plots of EMF vs. pH in the range of pH 3-9 (A, B, C) and pH 9-12 (D, E, F).
2.3.3 The IrO$_2$ NFs modified screen-printed electrodes (IrO$_2$ NFs-Nafion/SPE) toward both glucose and pH monitoring

Screen-printed electrode (SPE) has been widely used in commercial electrochemical test strips such as glucose test strips. Thus to get one step closer to real product configuration, IrO$_2$ NFs were further employed to modify SPEs, thus developing an electrochemical test strip sensor toward both glucose and pH monitoring. A small reservoir was first built on the IrO$_2$-Nafion/SPE to hold small volume of solution for pH sensing and glucose sensing.

Standard buffer solution with pH values of 4.0, 7.0, and 10.0 were first used to establish the calibration curve for IrO$_2$ NFs-Nafion/SPE. As shown in Figure 2.11A, pH-dependent EMF was observed with good linearity and stability. The Nernst constant of IrO$_2$ NFs-Nafion/SPE based pH detection is slightly smaller than that of IrO$_2$-Nafion/GCE, which may be attributed to slow diffusion related with non-stirring solution on the test strip. As a further demonstration of the developed dual sensor, 0.1 M NaOH (pH 13) solution was loaded onto the small reservoir on the IrO$_2$ NFs-Nafion/SPE. The pH value of the loaded 0.1 M NaOH solution was performed before glucose detection. According to the pH calibration curve established from three standard buffer solutions in Figure 2.11A, the pH value of 0.1 M NaOH was determined to be 12.95 using the developed the IrO$_2$ NFs-Nafion/SPE, which is very close to the theoretical value of pH 13 for 0.1 M NaOH solution, indicating the accuracy of the IrO$_2$ NFs-Nafion/SPE in pH sensing. The IrO$_2$ NF-Nafion/SPE sensor was further tested with various glucose concentrations using chronoamperometric method. The glucose with different final concentration was first added into 0.1 M NaOH solution on the sensor and then the current changes with time was recorded. The results were showed in Figure 2.11C. Taking the readings at 0.5 s to plot current vs. glucose concentration, the corresponding calibration curve was presented in Figure 2.11C. The IrO$_2$ NFs Nafion/SPE sensor showed good linear relationship for glucose in the tested range from 0 mM to 16 mM with $R^2=0.9889$. In conjunction with pH detection, this study demonstrates that the developed IrO$_2$ NFs-Nafion/SPE can serve as a dual sensor for both pH and glucose detection, which opens an avenue in the development of novel dual sensing system.
Figure 2.11 (A) EMF vs. time for IrO$_2$ NFs modified screen-printed electrode upon the addition of pH 4.0, 7.0, and 10.0 standard buffer solutions and 0.1 M NaOH solution, respectively. Inset shows the pH calibration curve based on EMF values from the three standard buffer solutions; (B) Chronoamperometric response of IrO$_2$ NF-Nafion/SPE for different glucose concentrations. (C) The corresponding calibration curve for glucose.

2.4. Conclusions

In summary, a novel dual electrochemical sensor based on electrospun IrO$_2$ nanofibers modified glassy carbon electrode and screen-printed carbon electrode was fabricated. Due to the pH sensitivity and glucose oxidation capability of IrO$_2$ NFs, the developed sensor was applied for both non-enzymatic glucose sensing and pH monitoring. Not only does it possess good sensitivity, a low detection limit and a wide linear range, and good selectivity and reproducibility in glucose sensing, but also maintain good pH sensitivity, rapid response and impressive reversibility in pH monitoring. The origin of glucose catalytic activity of the as-prepared IrO$_2$ NFs is attributed to high-temperature annealing enabled crystallinity. Moreover, the developed dual sensor was applied to detect both glucose in human serum samples and the pH value of real samples with remarkable accuracy. All these features indicate that the as-prepared IrO$_2$ NFs is a new class of multifunctional sensing material in the development of dual sensor.
Chapter 3

Dual Functional Rhodium Oxide Nanocorals Enabled Sensor for both Non-enzymatic Glucose and Solid-state pH Sensing
Abstract
Both pH-sensitive and glucose-responsive rhodium oxide nanocorals (Rh$_2$O$_3$ NCs) were synthesized through electrospinning followed by high-temperature calcination. The as-prepared Rh$_2$O$_3$ NCs were systematically characterized using various advanced techniques including scanning electron microscopy, X-ray powder diffraction and Raman spectroscopy, and then employed as a dual functional nanomaterial to fabricate a dual sensor for both non-enzymatic glucose sensing and solid-state pH monitoring. The sensing performance of the Rh$_2$O$_3$ NCs based dual sensor toward pH and glucose was evaluated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively. The results show that the as-prepared Rh$_2$O$_3$ NCs not only maintain accurate and reversible pH sensitivity of Rh$_2$O$_3$, but also demonstrate a good electrocatalytic activity toward glucose oxidation in alkaline medium with a sensitivity of 11.46 $\mu$A·mM·cm$^{-2}$, a limit of detection of 3.1 $\mu$M (S/N=3), and a reasonable selectivity against various interferents in non-enzymatic glucose detection. Its accuracy in determining glucose in human serum samples was further demonstrated. These features indicate that the as-prepared Rh$_2$O$_3$ NCs hold great promise as a dual-functional sensing material in the development of a high-performance sensor for both solid-state pH and non-enzymatic glucose sensing.

Keywords: rhodium oxide; dual sensor; nanocorals; non-enzymatic glucose detection; solid-state pH sensing
3.1. Introduction
As two of most successful sensors used in industry and academia, glucose sensor and pH sensor are of paramount importance in battling diabetes and probing acidity/alkalinity, respectively. On one hand, according to the data from World Health Organization in 2017, over 422 million adults suffer from diabetes. It has been a global health issue since last century with ~1.6 million deaths each year directly attributing to diabetes. Healthy ones typically have a blood glucose concentration ranging from 4.4-6.6 mM, while diabetes patients have significantly higher glucose concentration. Therefore, continuous or intermittent measurement of glucose level is of paramount importance for diabetic patients. Consequently it is not surprising that glucose sensors occupy around 85% of the biosensor market. Currently glucose sensors dominating the market are enzyme-based biosensors, relying on either glucose oxidase or glucose dehydrogenase [149]. However, the intrinsic instability of enzyme and the requirement of mild operating/storage conditions [19] could sacrifice the shelf life and the sensing performance of the glucose sensing strips. Therefore, it is of high necessity to develop non-enzymatic glucose sensors as an alternative. Up to date, various kinds of metal oxides have been extensively investigated for non-enzymatic glucose monitoring, including CuO [164, 177, 180], NiO [156, 193], Co₃O₄ [199, 254], MnO₂ [245], Mn₃O₄ [153], Fe₃O₄ [18], IrO₂@NiO [151], etc. Compared to metal or metal alloy based non-enzymatic glucose sensors [142], metal oxides [278] are superior in performance in the presence of high concentration of chloride ions [41], which could impair signal of the metal or metal alloy based sensing materials.

On the other hand, pH sensor has been employed as a routine instrument in research laboratories and various industrial sectors to probe the acidity or alkalinity of aqueous solutions due to the importance of pH values for the control of water quality and chemical reactions. Currently, glass membrane based electrode is the most widely used pH sensor but unfortunately suffers from the brittleness. Therefore, more rigid pH sensors have been proposed and developed as alternatives. Although ion-sensitive field-effect transistor and optical pH sensors have witnessed improved durability with early success, the potential high cost and poor performance limit their wider applications. Consequently, solid-state pH sensor, which measures the difference of electromotive
force (EMF) between sensing and reference electrodes, gradually becomes the trends in the development of next generation pH sensor due to its durability, low cost and miniaturization. In this regard, various solid-state metal oxides including IrO$_x$ [248], RhO$_2$ [249], SnO$_2$ [250, 251], RuO$_2$ [252, 253], etc.) have been exploited as potential sensing materials of solid-state pH sensors. Although both solid-state pH sensors and metal oxide based non-enzymatic glucose sensors have been extensively and individually studied, it still remains unmet challenge to develop a single sensing material for both non-enzymatic glucose and solid-state pH sensing. This is mainly attributed to the lack of both pH-sensitive and glucose-responsive sensing materials. Therefore, new functional materials or existing materials with new functionality should be developed and/or identified in order to accomplish aforementioned dual sensor concept.

As an element in Group-9 of the periodic table, rhodium and its oxide have attracted rare attention regarding its direct glucose oxidation performance though rhodium oxide was reported to possess pH sensitivity [249]. Group-9 includes cobalt [151], rhodium (Rh), iridium (Ir), and meitnerium (Mt). In our previous studies [259] and other reports [279, 280], iridium oxide and cobalt oxide have been applied in the development of solid-state pH sensors, while cobalt oxide (Co$_3$O$_4$) nanofibers was reported by our group for non-enzymatic glucose detection [199]. According to the hypothesis that the oxides from the same group elements share similar behavior, one can expect that rhodium oxide should possess both pH-sensitive and glucose-responsive properties.

Herein, this study aims to develop a dual electrochemical sensor for both glucose and pH sensing using a single sensing material. Rh$_2$O$_3$ nanocorals (Rh$_2$O$_3$ NCs) were prepared by electrospinning followed by high temperature calcination, which possessed glucose oxidation activity without sacrificing its pH sensitivity, thus offering a unique sensing material in the development of a dual sensor for both glucose and pH sensing. The experiment results show that the Rh$_2$O$_3$ NCs based dual sensor exhibits good pH sensitivity with excellent reversibility in pH titration, while it also possesses a sensitivity of 11.46 \( \mu \text{A} \cdot \text{mM}^{-1} \cdot \text{cm}^{-2} \), a limit of detection of 3.1 \( \mu \text{M} \), a good reproducibility, and a reasonable selectivity against the common interferents in non-enzymatic glucose detection. Its good accuracy for detecting glucose in human serum sample was also
evaluated and validated. All these features indicate that the high-temperature calcined Rh$_2$O$_3$ NCs are a promising multifunctional sensing material in the development of an integrated solid-state pH sensor and non-enzymatic glucose sensor.

3.2. Experimental Section

3.2.1. Materials

Rhodium chloride hydrate (RhCl$_3$·3H$_2$O) was obtained from Alfa Inorganics. D- (+)-glucose, acetaminophen (4-AP), ascorbic acid (AA), and uric acid (UA) were purchased from Acros Organics. Sodium hydroxide (NaOH) was provided by Fisher Scientific. Poly (vinyl pyrrolidone) (PVP, MW=1,300,000), human serum (from male AB clotted whole blood) and Nafion® perfluorinated resin solution (20% in lower aliphatic alcohols and water) were purchased from Sigma-Aldrich. All chemicals used were analytical grade and utilized without further purification. All aqueous solutions were prepared with deionized water (18.2 MΩ-cm) generated by a Barnstead water system.

3.2.2 Synthesis of Rh$_2$O$_3$ NCs

In a typical process, 0.08 g of RhCl$_3$·3H$_2$O was dissolved in 4 mL of ethanol solution, followed by the addition of 0.5 g PVP. The mixed solution was under magnetic stirring for overnight. The as-prepared homogenous solution was then electrospun using 23-gauge needle with a flow rate of 0.3 mL/h at an applied voltage of 20 kV over an aluminum foil collector of 7 cm distance [281]. The RhCl$_3$/PVP nanofibers collected on the collector were then peeled off. After 4 hours pre-dry step at 95 °C in an oven, the as-prepared RhCl$_3$/PVP precursory nanofibers were calcined under air atmosphere at 700 °C for 3 hours with a ramp-up speed at 2 °C/min. The furnace was then allowed to naturally cool down to room temperature and the as-prepared Rh$_2$O$_3$ NCs were collected.

3.2.3 Preparation of Rh$_2$O$_3$ NCs modified glassy carbon electrodes

First, the glassy carbon electrode (GCE, diameter of 3 mm) was polished with 1 µm and 50 nm alumina slurries in sequence, and then rinsed with DI water. Finally, the electrode was sonicated in ethanol and deionized water, dried at room temperature, and ready for modification. For GCE modification, 5 mg of Rh$_2$O$_3$ NCs were mixed with 1 mL of ethanol and sonicated for 40 mins. After that 8 µL of Rh$_2$O$_3$ NCs suspension was dropped
onto the surface of GCE. In order to entrap Rh$_2$O$_3$ NCs on GCE, 2 μL of Nafion solution (1.0 wt% in ethanol) was further cast onto the top of Rh$_2$O$_3$ NCs and dried in air. The as-prepared electrode is denoted as Rh$_2$O$_3$ NCs/Nafion/GCE. As a comparison, Nafion-coated glassy carbon electrode (Nafion/GCE) was also prepared as the control electrode following a similar procedure. Before use, each electrode was submerged into DI water to allow Nafion membrane to be fully swelled. All experiments were repeated at least 3 times to ensure the reproducibility.

3.3. Results and Discussion

3.3.1 Morphological and structural characteristics

The morphologies of the as-prepared RhCl$_3$/PVP precursory nanofibers and Rh$_2$O$_3$ NCs are first investigated using SEM and presented in Figure 3.1. As shown, the RhCl$_3$/PVP precursory nanofibers shows typical fibrous structure with an average diameter of 131 nm. However, after calcination, notably morphology change was observed after the degradation of PVP and decomposition of RhCl$_3$. The final Rh$_2$O$_3$ product displays a typical nanocoral structure with an average size of 321 nm. The increase of the size after calcination may be attributed to the migration of Rh$^{3+}$ and subsequent agglomeration of rhodium oxide during the process of PVP decomposition.

Figure 3.1. Typical SEM images of (A) electrospun RhCl$_3$/PVP precursory nanofibers and (B) Rh$_2$O$_3$ nanocorals after calcination of electrospun RhCl$_3$/PVP precursory nanofibers at 700 °C for 3 hours. Scale bar = 1 μm.

The composition and crystal structure were further characterized by XRD pattern, as shown in Figure 3.2. The XRD pattern of the as-prepared Rh$_2$O$_3$ NCs can be well-
assigned to the orthorhombic crystalline $\beta$-Rh$_2$O$_3$ (JCPDS No. 00-043-0009), which was revealed by peaks at 2$\theta$ values of 23.81°, 32.83°, 34.10°, 34.82°, 41.25°, 42.87°, 48.68°, 49.62°, 53.96°, 55.71°, 59.61°, 62.06°, 62.82°, 71.04°, 73.53°, 76.72°, corresponding to (004), (020), (114), (200), (024), (204), (220), (008), (131), (118), (134), (208), (135), (137), (400), (331) crystal planes, respectively [281]. No other impurities could be detected in the XRD pattern of Rh$_2$O$_3$ NCs, indicating that pure Rh$_2$O$_3$ phase is obtained.

Figure 3.2. X-ray powder diffraction pattern for the calcined Rh$_2$O$_3$ nanocorals.

Raman spectra were also employed to examine the difference between the RhCl$_3$/PVP precursory nanofibers and the final Rh$_2$O$_3$ NCs. As shown in Figure 3.3, four peaks located at 277 cm$^{-1}$, 424 cm$^{-1}$, and 565 cm$^{-1}$, 614 cm$^{-1}$ corresponds to $E_g$, $E_g$, $A_{1g}$ and $E_g$ modes of the crystalline Rh$_2$O$_3$, respectively [281, 282]. There was no prominent peak observed in the Raman spectrum of RhCl$_3$/PVP precursory nanofibers, which further indicated the formation of $\beta$-Rh$_2$O$_3$ after high temperature annealing process.
Figure 3.3. Raman spectra of RhCl₃/PVP precursory nanofibers (blue trace) and the as-prepared Rh₂O₃ nanocorals (red trace), respectively.

3.3.2 Rh₂O₃ NCs modified glassy carbon electrode for pH sensing

The as-prepared Rh₂O₃ NCs/Nafion/GCE was first investigated for its pH sensitivity in pH titration using universal buffer. Rhodium oxide is documented for its electromotive force (EMF) variation with pH change in aqueous condition [249]. The pH sensing mechanism of rhodium oxide can be ascribed to the attachment or the release of hydroxide ion on the rhodium oxide surface in basic and acidic environment, thus resulting in EMF change. To further demonstrate the as-developed Rh₂O₃ NCs/Nafion/GCE as a solid-state pH sensor, pH titration was conducted from pH 3 to pH 9 and then back to pH 3 as well as from pH 10 to pH 13 and then back to pH 10. The corresponding EMF value was recorded in real-time format and shown in Figure 3.4A and 3.4C. Meanwhile, a commercial Accumet AB15 pH meter was used to monitor the actual pH value of the buffer solution. One can see that the sensor responded to pH variation rapidly and the relative stable potential were typically obtained within 10 seconds, which is better than the stabilizing time for commercial pH meter. The calculated Nernst constants are 43.8 mV/pH (between pH 3 and pH 9) and 27.1 mV/pH (between pH 10 and pH 13), indicating that the as-prepared Rh₂O₃ NCs has good performance in acidic and mild basic environment. The deviation of the performance in
strong basic environment may be attributed to saturation of Rh$_2$O$_3$ surface for hydroxyl ion interaction. In addition, the observed hysteresis, which is represented by the difference of the electrochemical potentials at the same pH level, can be attributed to a number of factors such as slightly different thermodynamic equilibrium established at the same pH during titration, which may result from the nanostructures and/or the hydration degree on the Rh$_2$O$_3$ NCs. This study further corroborates the claim that the calcinated Rh$_2$O$_3$ NCs still maintains the good pH sensitivity.

Figure 3.4. Electromotive force (EMF) vs. time curves for the Rh$_2$O$_3$ NCs/Nafion/GCE during reversible pH titration cycles in the range of pH 3.0-9.0 (A) and pH 10-13 (C) and their corresponding plots of EMF vs. pH in the range of pH 3.0-9.0 (B) and pH 10-13 (D).

3.3.3. Rh$_2$O$_3$ NCs modified glassy carbon electrode for non-enzymatic glucose detection

To explore the applicability of Rh$_2$O$_3$ NCs for glucose oxidation in alkaline medium, the CVs of the Rh$_2$O$_3$ NCs/Nafion/GCE in neutral PBS buffer (Figure 3.6A, traces a and
b) and 0.1 M NaOH (Figure 3.6A, traces c and d) were recorded in the presence and absence of 5 mM glucose ranging from -0.5 V to +0.7 V vs. Ag/AgCl at a scan rate of 100 mV/s. As shown, there is no glucose oxidation observed on the Rh₂O₃ NCs/Nafion/GCE in PBS buffer (Figure 3.6A, traces a and b), while significant glucose oxidation was observed on the same electrode in 0.1 M NaOH solution with an onset potential of ca. +0.325 V. This study indicates the requirement of hydroxyl ion in glucose oxidation on Rh₂O₃ NCs. Before other experiments, the loading of Rh₂O₃ NCs on GCE was optimized using CV first. The corresponding results are presented in Figure 3.5. With the increase of Rh₂O₃ NCs loading, the response from glucose oxidation increased initially and then reached the maximum value at the loading of 40 µg Rh₂O₃ NCs. Therefore, 40 µg loading was applied for subsequent experiments.

\[ \text{Normalized Current (a.u.)} \]

\[ \begin{array}{c|c}
\text{Weight / µg} & 0.2 & 0.3 & 0.4 & 0.5 & 0.6 & 0.7 & 0.8 & 1.0 \\
\hline
10 & & & & & & & & \\
20 & & & & & & & & \\
30 & & & & & & & & \\
40 & & & & & & & & \\
50 & & & & & & & & \\
60 & & & & & & & & \\
70 & & & & & & & & \\
\end{array} \]

*Figure 3.5. The normalized current response (readings at 0.4 V vs Ag/AgCl) of the Rh₂O₃ NCs/Nafion/GCE with different loading of Rh₂O₃ NCs in the presence of 5 mM glucose (the electrolyte is 0.1 M NaOH solution).*
To elucidate the role of Rh$_2$O$_3$ NCs in glucose oxidation, the CVs of the Nafion/GCE (Figure 3.6B, traces e and f) and Rh$_2$O$_3$ NCs/Nafion/GCE (Figure 3.6B, traces g and h) were further recorded in 0.1 M NaOH in the presence and absence of 5 mM glucose. In the presence of glucose, there is no obvious peak observed on the Nafion/GCE when compared to the CV in the absence of glucose. However, glucose was oxidized on the Rh$_2$O$_3$ NCs/Nafion/GCE. According to the mechanism proposed in the literature based on various metal oxides, the glucose oxidation on Rh$_2$O$_3$ NCs in alkaline solution can be presumably expressed as following reactions:

$$\text{Rh}_2\text{O}_3 + 2\text{OH}^- + \text{H}_2\text{O} \rightarrow 2\text{RhO(OH)}_2 + 2e^-$$

$$2\text{RhO(OH)}_2 + 2\text{glucose} \rightarrow \text{Rh}_2\text{O}_3 + 2\text{glucolactone} + 3\text{H}_2\text{O}$$

Furthermore, the effect of scan rates on the oxidation and reduction peak currents were studied and the corresponding result was presented in Figure 3.7A. One can see that the redox peak currents increased linearly with the scan rate (Figure 3.7B), indicating a typically surface-controlled electrochemical process. As the scan rate varied, however, the anodic peak position and cathodic peak position did not shift, indicating that rhodium oxide involved in a quasi-reversible reaction.
Before amperometric detection of glucose using the Rh$_2$O$_3$ NCs/Nafion/GCE, the applied potential was further optimized. Therefore, hydrodynamic voltammetry experiment was carried out at different potentials ranging from 0.52 V to 0.66 V with an increment of 0.04 V and the corresponding result was presented in Figure 3.8. One can see the maximal response of the Rh$_2$O$_3$ NCs/Nafion/GCE toward the addition of 100 µM glucose was obtained at +0.62 V, which was employed for subsequent amperometric detection.

Figure 3.8. Normalized hydrodynamic voltammetry for 100 µM glucose in 0.1 M NaOH solution at the Rh$_2$O$_3$ NCs/Nafion/GCE.
Figure 3.9. (A) Amperometric response of the Rh$_2$O$_3$ NCs/Nafion/GCE to successive addition of glucose at an applied potential of +0.62 V (vs. Ag/AgCl). (B) The corresponding calibration curve (dots) and the Langmuir isothermal fitting curve (red solid line).

Figure 3.9A shows the typical amperometric responses of the developed sensor to successive injection of glucose in 0.1 M NaOH. Inset of Figure 3.9A shows the lower detection range at the Rh$_2$O$_3$/Nafion/GCE. A well-defined, step-wise and stable amperometric response within 5 s can be observed on the Rh$_2$O$_3$ NCs/Nafion/GCE upon successive addition of glucose into 0.1 M NaOH solution. The corresponding calibration curve (current vs. glucose concentration) was shown in Figure 3.9B. With the increase of glucose concentration, the amperometric current increased proportionally and displayed a concentration-dependent behavior. The electrochemical oxidation of glucose on Rh$_2$O$_3$ NCs is a surface catalytic reaction, which is typically described by Langmuir isothermal theory [199]. Therefore, Langmuir isothermal equation was adapted to fit the experimental data. The corresponding fitting curve was showed in Figure 3.9B, with a calculated $R^2=0.9997$. The fitting curve can be represented by an equation as follow:

$$I(\mu A) = \frac{0.8133C_{glucose}(mM)}{1 + 0.0651C_{glucose}(mM)}$$

The limit of detection (S/N=3) was calculated to be 3.1 µM, while the sensitivity of the modified Rh$_2$O$_3$ NCs/Nafion/GCE was 11.46 µA·mM$^{-1}$·cm$^{-2}$. The sensing
performance (e.g., the sensitivity and/or the limit of detection) are comparable to most of other non-enzymatic glucose sensors (Table 3.1).

Table 3.1. Comparison of various non-enzymatic glucose sensors

<table>
<thead>
<tr>
<th>Materials</th>
<th>LOD</th>
<th>Linear Range</th>
<th>Sensitivity (µA mM⁻¹ cm⁻²)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt-Au</td>
<td>3.2 µM</td>
<td>0-22 mM</td>
<td>24.6</td>
<td>[71]</td>
</tr>
<tr>
<td>NiO-CdO</td>
<td>0.35</td>
<td>0-6.37 mM</td>
<td>212.71</td>
<td>[258]</td>
</tr>
<tr>
<td>Cu nanowires</td>
<td>35 nM</td>
<td>Up to 3 mM</td>
<td>48.35</td>
<td></td>
</tr>
<tr>
<td>Co₃O₄</td>
<td>0.97 µM</td>
<td>Langmuir-</td>
<td>36.25</td>
<td>[156]</td>
</tr>
<tr>
<td>NiO-Au</td>
<td>1.32 µM</td>
<td>Isothermal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MnO₂/MWCNT</td>
<td>1 mM</td>
<td>0-28 mM</td>
<td>33.19</td>
<td>[270]</td>
</tr>
<tr>
<td>Pt-Ir</td>
<td>1 mM</td>
<td>0-10 mM</td>
<td>93.7</td>
<td>[283]</td>
</tr>
<tr>
<td>IrO₂@NiO</td>
<td>0.31 µM</td>
<td>0.5 µM-2.5 mM</td>
<td>1439.4</td>
<td>[151]</td>
</tr>
<tr>
<td>Polyaniline-Cu(I) composite</td>
<td>-</td>
<td>0.4-4.0 mM</td>
<td>0.4744</td>
<td>[65]</td>
</tr>
<tr>
<td>Rh₂O₃ NCs</td>
<td>3.10 µM</td>
<td>Langmuir-</td>
<td>11.46</td>
<td>Present</td>
</tr>
</tbody>
</table>

The selectivity of the Rh₂O₃ NCs/Nafion/GCE was also investigated against normally co-existing interfering species with glucose such as 4-acetaminophen (4-AP, a pain reducing drug), ascorbic acid (AA) and uric acid (UA). The endogenous concentration of ascorbic acid, uric acid, and acetaminophen are typically at the levels of 0.125 mM, 0.33 mM and 0.13 mM, respectively [199, 284, 285], while the concentration of glucose in blood varies from 4.4 mM to 6.6 mM in healthy people. Thus, the amperometric signal of glucose on the Rh₂O₃ NCs/Nafion/GCE was compared with those of 4-AP, UA, and AA at 10 to 1 concentration ratio. Compared to that of 100 µM glucose, 10 µM UA did not result in significant interference (~11%). Although 10 µM 4-AP and AA resulted in ~50% and ~46% response, respectively, one can expect that the actual interference from 4-AP and AA in real sample is kind of mild because glucose concentration is at least 30-fold
higher than 4-AP and AA. Such claim was partially corroborated by glucose detection in human serum samples conducted in next section.

![Figure 3.10](image)

**Figure 3.10.** (A) The amperometric response of the Rh$_2$O$_3$ NCs/Nafion/GCE to successive addition of 10 µL of human serum plasma and 10 µL of 10 mM glucose. (B) Glucose concentration in human serum sample determined by commercial glucose meter (OneTouch® UltraMini, LifeScan, CA) and the developed sensor in this study.

As a real application, the detection of glucose in humans serum sample was also conducted using the as-developed glucose sensor. Figure 3.10A shows the response of the developed sensor upon the sequential injection of human serum and standard 10 mM glucose solution. According to the calibration curve, the glucose concentration in human serum plasma is calculated to be 5.97 mM, in good agreement with the glucose concentration of 6.00 mM determined by using commercial glucose meter (OneTouch UltraMini, LifeScan, Inc, CA) (Figure 3.10B). Such good agreement indicates the accuracy of the developed sensor. The reproducibility of the developed biosensor for glucose detection was also investigated. The relative standard deviation (R.S.D) of 1.74% (n=3) for 100 µM glucose demonstrated good intra-electrode reproducibility. In addition, the good inter-electrode reproducibility was characterized by the low R.S.D. (1.83%) in the response of 100 µM on four Rh$_2$O$_3$/Nafion/GCE sensors. In conjunction with the aforementioned pH sensing results, these results endow the as-prepared Rh$_2$O$_3$ NCs being a promising dual-functional material in the construction of a dual sensor for both solid-state pH sensing and non-enzymatic glucose sensing.
3.4 Conclusions

As a new class of multifunctional material, Rh$_2$O$_3$ NCs were synthesized using electrospinning followed by high-temperature calcination, and then employed as the sensing element to fabricate a novel dual glucose and pH sensor in this study. The as-prepared Rh$_2$O$_3$ NCs were systematically characterized using scanning electron microscopy, X-ray diffraction, and Raman spectroscopy, while the electrochemical and electrocatalytic performance of the Rh$_2$O$_3$ NCs based dual sensor toward pH and glucose sensing were evaluated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively. The Rh$_2$O$_3$ NCs not only possess good and reversible pH sensitivity as expected, but also demonstrate the electrocatalytic activity toward glucose. This unique dual functionality enables us to develop a sensor which can be applied for both non-enzymatic glucose and solid-state pH sensing. The experiment results show that the Rh$_2$O$_3$ NCs based dual sensor exhibits a Nernst constant lower than a theoretical value with excellent reversibility in pH titration, while it also possesses a sensitivity of 11.46 µA·mM·cm$^{-2}$, a limit of detection of 3.1 µM (S/N=3), and a reasonable selectivity against various interferents in non-enzymatic glucose detection. Its good accuracy for detecting glucose in human serum sample was also demonstrated. These features indicate that the as-prepared Rh$_2$O$_3$ NCs hold great promise as a dual-functional sensing material in the development of a high-performance sensor for both solid-state pH and non-enzymatic glucose sensing.
Chapter 4

Nitrogen-doped Hollow Co$_3$O$_4$ Nanofibers for both Improved Non-enzymatic Glucose Sensing and Solid-state pH Sensing
Abstract:

Nitrogen-doped hollow cobalt oxide nanofibers (Co$_3$O$_4$ NFs) with both glucose catalytic activity and pH sensitivity were fabricated through core-sheath electrospinning technique, followed by calcination. The as-developed nitrogen-doped hollow Co$_3$O$_4$ NFs were thoroughly characterized using various techniques, including X-ray powder diffraction, scanning electron microscopy, transmission electron microscopy, Raman spectroscopy, thermogravimetric analysis, and then employed to fabricate a dual electrochemical sensor for both pH sensing and glucose sensing. The pH sensitivity of the developed nitrogen-doped hollow Co$_3$O$_4$ NFs demonstrated a Nernst constant of 31.1 mV/pH in the pH range of 3.0~9.0 and 41.1 mV/pH in the pH range of 9.0~13.0, respectively. The developed hollow cobalt oxides nanofibers sensor also possesses glucose sensitivity of 87.67 µA mM$^{-1}$ cm$^{-2}$, the limit of detection of 0.38 µM (S/N=3), and a reasonable selectivity against several common interferents in non-enzymatic glucose determination. High accuracy for monitoring glucose in human serum sample was also demonstrated. These features indicate that the as-synthesized nitrogen-doped hollow cobalt oxides nanofibers hold great potential in the development of a unique dual sensor for both solid-state pH sensing and superior non-enzymatic glucose sensing.
4.1. Introduction

As two most popular sensors, pH sensor and glucose sensor play important roles in our daily life. On one hand, probing the acidity/alkalinity of aqueous solutions is of paramount importance in monitoring water quality and controlling chemical reactions. During the past decades, several pH sensing techniques have been developed. As one widely used low-cost pH sensor in the laboratories, paper-based pH test strips can cover a wide pH range, e.g. pH 1~14 with relative low resolution (e.g. 0.5 pH). However, its determination of pH value is based upon subjective decision of colorimetric result. Consequently, it is only suitable for qualitative pH screening. To quantitatively detect pH value, glass membrane pH electrode is developed as one of the most widely used pH sensors with a resolution of ±0.05 pH. However, it suffers from the brittleness as all other glassware face. To address the brittleness and improve the durability and accuracy, ion-selective field effect transistors (ISFETs) based pH sensor was developed in 1980s’ and has been continuously improved with super high resolution[286] through the conjunction with different metal oxides[251, 287, 288]. However, the high cost and relatively small Nernst-constant hinder its broader application. As an alternative pH sensing technology, a solid-state pH sensor has drawn extensive attention in terms of its rigidness, stable performance in harsh environment and low cost. In this regard, different solid-state metal oxides, including IrO$_x$ [248], RhO$_2$ [249], SnO$_2$[251], RuO$_2$ [253, 289] etc., have been explored as pH-sensing element in the development of solid-state pH sensors.

On the other hand, measuring the concentration of glucose in human blood [290] or saliva[151] is of paramount significance for diabetes patients. World widely, 422 million adults suffer from diabetes according to the data from World Health Organization (WHO). Moreover, over 1.6 million deaths are directly attributed to diabetes diseases every year. Therefore, it is critical for diabetes patients to monitor and manage their blood glucose level intermittently or through continuous blood glucose monitoring. Typically, a healthy person has his/her body of glucose at the range of 4.4 mM to 6.6 mM. However, diabetes patients often have higher concentration of glucose than healthy ones. Up to date, the enzyme-based glucose test strips occupy over 85% of glucose
sensing market. However, the performance of those test strips are subjected to the intrinsic property of “fragile” glucose oxidase [19] or glucose dehydrogenase [291]. From the standpoint of enzyme sensitivity to environmental factors (e.g. temperature and pH), the accuracy of enzyme-based test strips could vary notably due to extreme temperature condition from weather and blood pH fluctuation from person to person. Alternatively, non-enzymatic glucose test strips, typically operating in alkaline environment, are proposed and developed to address aforementioned challenges. Up to date, various kinds of metal oxides have been exploited in this regard, including CuO[163-165, 168, 170, 171, 174, 175, 177, 178, 180-183, 185, 187, 189, 238, 239], NiO[151, 155, 156, 193, 195], Co3O4[87, 174, 199, 201-203, 205-207], MnO2[245], Mn3O4[153], Fe3O4[18], IrO2, Rh2O3[292], SnO2[247], TiO2[70] etc. Compared to noble metal or noble metal alloy, metal oxides based non-enzymatic glucose detection is free of chloride fouling at high chloride concentration, which is commonly encountered in blood sample test.

Both solid-state pH sensors and metal oxides-based enzyme-free glucose sensors have been extensively but individually studied. To construct a dual pH and glucose sensor, single sensing material possessing both functions is required. Therefore, there is a continuous effort to seek such multifunctional materials. In our previous report[292], we have demonstrated that both iridium oxide and rhodium oxide possess pH- and glucose-sensitivity. Iridium, rhodium and cobalt belong to Group-9 in periodic table. According to the assumption that the same group of elements and their derivatives share similar reactivity and property, cobalt oxide is a potential candidate possessing both pH- and glucose-sensitivity.[199],[280],[279]

Herein, this study focuses on developing an electrochemical sensor which can be applied for both pH sensing and glucose sensing using nitrogen-doped hollow cobalt oxide nanofibers. The sensing materials were prepared by a coaxial electrospinning technique followed by an annealing process. The experiment results show that the as-prepared dual sensor exhibits good sensitivity, selectivity, repeatability in glucose sensing as well as in pH titration experiment. Its high accuracy for monitoring glucose in human serum sample was also demonstrated. These features indicate that the as-synthesized nitrogen-doped
hollow cobalt oxides nanofibers hold great potential in the development of a unique dual sensor for both solid-state pH sensing and superior non-enzymatic glucose sensing.

4.2. Experiment

4.2.1 Chemical reagent
Cobalt nitrate hexahydrate (Co(NO$_3$)$_2$·6H$_2$O) were purchased from Fisher Scientific. Human serum (from male AB clotted whole blood), Nafion® 117 solution (purum, ~5% in a mixture of lower aliphatic alcohols and water) and Poly(vinyl pyrrolidone) (PVP, MW=1,300,000) were obtained from Sigma-Aldrich. Ascorbic acid, uric acid, ethanol (200 proof) and D-(+)-glucose and sodium hydroxide (NaOH, pellets) were supplied by Acros Organics. 0.1 M pH 7.4 phosphate buffer solution was prepared by diluting commercial 10× Phosphate buffer saline. Glucose solutions with different concentrations were diluted from stock solution (1 M). Conductor paste (Materials DUPONT Microcircuit Materials Prod: BQ226 LOT: YFF175) and thinner ether were purchased from DuPont to prepare carbon paste electrode. All aqueous solutions were prepared with deionized water (18.2 MΩ cm) generated by a Barnstead water system.

4.2.2 Preparation of Core-shell Co$_3$O$_4$ NFs nanofibers

Scheme 4.1 shows coaxial-tube spinneret used to generate the core-shell nanofibers for calcination. The outer diameter of the coaxial spinneret was 14-gauge while the inner diameter of the spinneret was 28-gauge. The liquid from the outer spinneret (A) was used to encapsulate the liquid from inner spinneret (B) to form the Taylor cone. Two solutions
A and B were prepared following our former report with minor modification[199].

Scheme 4.1. Electrospun set-up for fabrication of precursor of Co(NO$_3$)$_2$/PVP nanofibers by using a coaxial spinneret.

In brief, 0.8 g Co(NO$_3$)$_2$·6H$_2$O was dissolved in 9.30 mL ethanol and 1.86 g PVP was dissolved in fully mixed solution, denoted as solution A. Meanwhile, 1.2 g PVP was dissolved in 6.10 mL ethanol with stirring, denoted as solution B. The as-prepared homogenous solutions (A and B) were then electrospun using the T-shape coaxial spinneret with a flow rate of 0.075 mL/h (A in the core) and 0.3 mL/h (B in the shell) controlled by two syringe pumps, respectively. An applied voltage of 25 kV was applied over an aluminum foil with a collecting distance of 10 cm. The electrospinning process was carried out under ambient environment with humidity varied from 16%-20% controlled by a dehumidifier. The nanofibers collected on aluminum foil were then dehydrated at 90 °C for 3 hours and calcined at 500 °C for 6 h in order to remove the polymer in the core and generate Co$_3$O$_4$ shell, thus forming hollow Co$_3$O$_4$ nanofibers.

4.2.3 Preparation of core-shell Co$_3$O$_4$ modified glassy carbon electrode for glucose sensing
4.2.3 Preparation of N-doped hollow Co$_3$O$_4$ nanofibers modified glassy carbon electrode for glucose and pH sensing

First, the glassy carbon electrodes (GCE, diameter of 3 mm) were polished with alumina slurries with the size of 1 µm and 50 nm in sequence, and then these electrodes were cleaned by ultra-sonic bath with acetone, ethanol and deionized water for 5 mins each. Next, a stream of nitrogen was used to purge the electrodes for drying. For the purpose of glucose sensing modification, 7 mg of N-doped hollow Co$_3$O$_4$ nanofibers (NH-Co$_3$O$_4$ NFs) were mixed with 1 ml of ethanol and ultra-sonic for 40 mins. Such concentration of NH-Co$_3$O$_4$ NFs was calculated according to the optimal NH-Co$_3$O$_4$ NFs loading on glassy carbon electrode (GCE) determined by cyclic voltammetry technique in the presence of 5 mM of D-glucose (Fig. 4.1). For GCE modification, 5 µL of 7 mg/mL NH-Co$_3$O$_4$ NFs were drop-cast onto GCE and dried. Following that, the same volume of Nafion (1.0 wt% in ethanol) was subsequently drop-cast onto the top of the layer to entrap CNH-Co$_3$O$_4$ NFs and dried in air at room temperature, forming NH-Co$_3$O$_4$ NFs-Nafion/GCE electrode. Such NH-Co$_3$O$_4$ NFs-Nafion/GCE was further employed for pH titration experiment as well. As a comparison, Nafion-covered glassy carbon electrode (Nafion/GCE) was prepared by similar procedure without using N-doped hollow Co$_3$O$_4$ nanofibers. Before use, each modified electrode was dipped into DI water to allow swelling of Nafion membrane. All experiments were repeated in parallel for at least 3 times to assure the repeatability.
Fig. 4.1. The CVs peak current of the glassy carbon electrodes modified by different concentration of core-shell Co$_3$O$_4$ nanofibers (5 µL in ethanol) to the presence of 5 mM D-glucose in 0.1 M NaOH solution.

4.2.5 Instrumentation

A JEOL 6335F field-emission scanning electron microscope [107] was employed to examine the morphological property and the size of the precursor nanofibers and N-doped Co$_3$O$_4$ nanofibers. The X-ray powder diffraction patterns were obtained with a Scintag X-ray diffractometer with Cu Kα radiation (λ = 0.15406 nm) operating at 45 kV and 40 mA. Raman spectra of precursor nanofibers and N-doped Co$_3$O$_4$ NFs were collected using a Reinshaw Raman scope Micro-Raman with 514 nm wavelength laser. Cyclic voltammetry, amperometry and open circuit potential measurements were performed on a Model CHI 601C Electrochemical Workstation (CH Instruments, USA). All experiments were conducted by employing a standard three-electrode electrochemical cell, consisting of a working electrode (GCE dia. 3mm), an Ag/AgCl reference electrode, and a platinum electrode as counter electrode (dia. 3.0 mm). For amperometric glucose detection, all signals were recorded after current decay to a steady-state value and a
stirrer was used to provide convective mixing. For pH sensing, the pH-adjustable buffer was prepared using a recipe from a previous report[248]. Briefly, pH 3.0–9.0 solutions were universal buffers containing 10 mM potassium hydrogen phthalate, 10 mM phosphate, and 10 mM Tris, while pH 10.0–13.0 solutions contained 50 mM sodium carbonate, 10 mM borax and 140 mM NaCl. The pH adjustment was realized by addition of 1 M HNO$_3$ or 1 M NaOH.

4.3. Results and discussion

4.3.1 Structural characterization

The morphologies of the as-prepared PVP/Co(NO$_3$)$_2$-PVP core/sheath precursory nanofibers (Fig. 4.2B) and hollow Co$_3$O$_4$ nanofibers (Fig. 1C) were observed under SEM, and the averaged diameter was measured to be 842 ± 130 nm, and 294 nm ± 106 nm before and after calcination process, respectively.

![Figure 4.2](image-url)

Figure 4.2. (A) Scheme: Experimental set-up for fabrication of PVP/Co(NO$_3$)$_2$-PVP precursory nanofibers using a coaxial spinneret. (B) A representative SEM image of PVP/Co(NO$_3$)$_2$-PVP precursory nanofibers (scale bar, 10 µm); inset shows the image with a higher magnification of nanofibers (scale bar, 1 µm). (C) A representative SEM of N-doped hollow Co$_3$O$_4$ NFs (scale bar, 1 µm).
The as-prepared nanofibers after calcination were suspended in ethanol with the concentration of 0.1 mg/mL for the preparation of transmission electron microscopy [293]. Figure 4.3A reveals that the Co$_3$O$_4$ NF is hollow and displays a spiral shape, thus possessing a large surface to volume ratio and favoring the electrochemical sensing. Figure 4.3B, 2C and 2D show the element mapping of Co, O, and N, respectively. One can see that Co and O distribution is relatively uniform on the shell. The presence of N in the hollow Co$_3$O$_4$ NFs is originated from nitrogen content in PVP polymer. After calcination, a small portion of nitrogen was doped into the hollow Co$_3$O$_4$ NFs, resulting N-doped hollow Co$_3$O$_4$ NFs (denoted as NH-Co$_3$O$_4$ NFs). It is notable that the element cobalt and oxide formed shell structure.

![Figure 4.3](image_url)

*Figure 4.3. A TEM image of a single N-doped Co$_3$O$_4$ nanofiber (A), and the element mapping of Cobalt (B), Oxygen (C), and Nitrogen (D), respectively.*
The $d$-spacing values in Fig 4.4A of HRTEM were measured to be 0.322 nm, which was attributed to (220) planes of NH-Co$_3$O$_4$ NFs. The SAED patterns shown in Fig. 4.4B and clearly displayed several rings, which can be indexed to the planes of (111), (220), (311), (400) of Co$_3$O$_4$ cubic structure, respectively.

![HRTEM and SAED patterns](image)

Figure 4.4 Electron microscopy characterization of Nitrogen-doped NH-Co$_3$O$_4$ NFs: HRTEM images of NH-Co$_3$O$_4$ NFs (A) (scale bar 5 nm) and SAED (B) (scale bar 5.00 1/nm).

The crystal structure and composition were further studied by X-ray powder diffraction, as shown in Figure 4A. The XRD pattern of the as-prepared nitrogen-doped Co$_3$O$_4$ NFs can be well-assigned to the cubic crystalline cobalt dicobalt (III) oxide (Co$^{2+}$ [Co$_2^{3+}$]O$_4$)(JCPDS No. 80-1535), which was revealed by peaks at 2$\theta$ values of 31.09°, 36.63°, 38.39°, 44.60°, 59.19°, 64.95°, 77.28°, corresponding to (220), (311), (222), (400), (422), (440), (533) crystal planes, respectively[294]. No other impurities could be detected in the XRD pattern of NH-Co$_3$O$_4$ NFs, indicating that pure NH-Co$_3$O$_4$ NFs phase is obtained.
In order to analyze if carbon residue is presented or not after calcination process, thermogravimetric analysis [143] was carried out for the calcined NH-Co$_3$O$_4$ NFs. Figure 4.5B shows the TGA trace of NH-Co$_3$O$_4$ NFs with oxygen flow stream. As shown, no obvious weight% change was observed, indicating that no carbon trace left in the as-prepared hollow NH-Co$_3$O$_4$ NFs after calcination. Such claim was corroborated by
Raman spectrum of NH-Co$_3$O$_4$ NFs in which no G band was observed near \( \sim 1500 \text{ cm}^{-1} \) (Figure 5).

Figure 4.6A shows the Fourier transform-Infrared (FT-IR) spectra of the electrospun precursor nanofibers and the calcined hollow NH-Co$_3$O$_4$ NFs, respectively. Two sharp absorption peaks at 658 cm$^{-1}$ and 555 cm$^{-1}$ were observed in the spectrum of NH-Co$_3$O$_4$ NFs (red curve) but no characteristic peaks of PVP (e.g. 1650 cm$^{-1}$ for C=O and 1381 cm$^{-1}$ for NO$_3^-$) present. The two sharp peaks in red curve can be typically assigned to the Co-O bonds represented in Co (II, III) oxide[295]. The disappearance of the characteristic peaks of PVP and Co(NO$_3$)$_2$ indicates the decomposition of PVP and Co(NO$_3$)$_2$ during calcination.
Figure 4.6. (A) FTIR spectra of PVP/Co(NO$_3$)$_2$-PVP nanofibers (blue) and NH-Co$_3$O$_4$ NFs (red); (B) Raman spectra of NH-Co$_3$O$_4$ NFs (red) and PVP/Co(NO$_3$)$_2$-PVP nanofibers (blue).

Raman spectra were also employed to examine the difference between the PVP/Co(NO$_3$)$_2$-PVP precursory nanofibers and hollow NH-Co$_3$O$_4$ NFs. As shown in Figure 4.6B (red curve), four peaks recorded at 477.4 cm$^{-1}$, 518.0 cm$^{-1}$, 617.5 cm$^{-1}$, and 682.6 cm$^{-1}$, corresponds to $E_g$, $F^{1}_{2g}$, $F^{2}_{2g}$, and $A^1_g$ modes of the crystalline NH-Co$_3$O$_4$ NFs, respectively[296]. Comparing to hollow NH-Co$_3$O$_4$ NFs, the precursory nanofibers of PVP/Co(NO$_3$)$_2$-PVP did not show any prominent peak, indicating the formation of Co$_3$O$_4$ after high temperature treatment.
XPS spectroscopy was further applied to investigate the atomic orbital structure of NH-Co$_3$O$_4$ NFs. Initially, survey spectrum was collected as shown in Figure 4.7A, indicating that the as-synthesized Co$_3$O$_4$ NFs are mainly composed of cobalt and oxygen (carbon peak is shown due to the use of carbon tape substrate). The binding energy of C 1s peak was used as the standard to calibrate other peak position (Figure 4.7). The high-resolution spectra of O 1s, C 1s, and Co 2p are presented in Figure 6B, C and D, respectively. Figure 4.7B deconvoluted O 1s into two pairs of peaks with peak position at 529.55 eV, 530.33 eV, 531.74 eV, and 533.20 eV, which could be ascribed to O$_{L}$, O$_{L}$, O$_{V}$, and O$_{C}$ components. In O 1s, O$_{L}$ components centered at 529.55 eV and 530.33 eV can be attributed to the lattice oxygen in the NH-Co$_3$O$_4$ phase, the O$_{V}$ component at 531.74 eV is correlated with O$^{2-}$ ions in oxygen-deficient regions within the matrix of NH-Co$_3$O$_4$ (oxygen vacancies)[297], and the O$_{C}$ component centered at 533.20 eV associates with chemisorbed and dissociated oxygen species (O$_2^-$, O$^{2-}$, or O$^-$) and OH$^-$[298]. For the aspect of Co 2p doublet spectrum fitting, the two peaks of Co 2p 1/2 and Co 2p 3/2 centered at 795.4 eV and 780.25 eV with a separation of 15.15 eV are in good agreement with reported data of 15.28 eV[199] and 15.19 eV[299] and other report[300].

![Figure 4.7. (A) XPS survey spectrum of NH-Co$_3$O$_4$ NFs. High-resolution XPS spectra of O1s (B), C1s (C), and Co 2p (D), respectively.]

3.2. Electrocatalytical activity of hollow NH-Co$_3$O$_4$ NFs toward glucose oxidation

The CVs of the Nafion/NH-Co$_3$O$_4$ NFs/GCE were investigated in both neutral solution (0.1 M pH 7.4 phosphate buffer saline) and alkaline solution (0.1 M NaOH) in the range
from 0 V to 0.8 V vs. Ag/AgCl (Figure 4.8A). There were no pronounced oxidation or reduction peak observed in the neutral pH electrolyte while two pairs of well-defined redox peaks were acquired in alkaline solution with the peak positions located at 0.4 V (I), 0.3 V (II), 0.64 V (III), and 0.51 V (IV). These two pairs of redox peaks were evidenced for the involvement of hydroxide ion in the electrochemical redox reaction on the surface of hollow NH-Co₃O₄ NFs. According to literature reports [199] the pair of redox peaks I/II can be assigned to the reversible transition between Co₃O₄ and CoOOH, while the other pair of redox peaks III/IV can be ascribed to further transition between CoOOH and CoO₂ [301].
Figure 4.8. (A) CVs of the Nafion/NH$_2$Co$_3$O$_4$ NFs/GCE in 0.1 M NaOH solution (a) and in 0.1 M pH 7.4 phosphate buffer solution (b) at the scan rate of 100 mV/s; (B) CVs of the Nafion/NH$_2$Co$_3$O$_4$ NFs/GCE in 0.1 M NaOH solution at various scan rates of 20, 40, 60, 80, 100, 150, and 200 mV/s; (C) Plot of peak currents vs. scan rate.
Schematically, these two reversible reactions can be expressed as Eqs. (1) and (2) in below:

$$\text{Co}_3\text{O}_4 + \text{OH}^- + \text{H}_2\text{O} \leftrightarrow 3\text{CoOOH} + e^- \quad (1)$$
$$\text{CoOOH} + \text{OH}^- \leftrightarrow \text{CoO}_2 + \text{H}_2\text{O} + e^- \quad (2)$$

Peak current vs. scan rates were presented in Figure 7B. It is obvious that the peak currents and scan rate was in linear relationship in the range of 20 mV/s to 200 mV/s (Figure 7C), indicating a surface-controlled electrochemical reaction.

### 3.3. Electrooxidation of glucose at the Nafion/NH-Co3O4 NFs/GCE

The electrooxidation of glucose at Nafion/NH-Co3O4 NFs/GCE was then investigated in 0.1 M NaOH solution. Figure 8A demonstrates the CVs of Nafion/GCE and Nafion/NH-Co3O4 NFs/GCE in the absence and presence of 5 mM glucose. The Nafion/NH-Co3O4 NFs/GCE shows the onset potential at ca. +0.25 V (Figure 4.9A), demonstrating that the formation of CoOOH and CoO$_2$ in the range of peak I and peak III, respectively. On the contrary, no obvious response was found at Nafion/GCE. The result indicated that the catalytic property of the as-prepared Co$_3$O$_4$ nanofibers towards glucose oxidation in alkaline solution was related to CoOOH and CoO$_2$. In addition, as shown in Figure 8A, the current increase with the addition of glucose at peak III (CoOOH $\rightarrow$ CoO$_2$) was much stronger than that at peak I (Co$_3$O$_4$ $\rightarrow$ CoOOH), which may suggest that the electrooxidation of glucose is mainly mediated by CoOOH/CoO$_2$, rather than Co$_3$O$_4$/CoOOH in an alkaline solution. Therefore, the peak III potential (+0.64 V) was applied for the following amperometric detection. According to the book of “Electrochemical Methods Fundamentals and Applications ” by A.J. Bard and L.R. Faulkner [302], the discussion about surface reaction (as we demonstrated from Figure 4.8B and 4.8C), equation $\Delta E_{p,1/2} = 90.6/n$ mV (25°C) can be adopted to calculate the number of electron transferred (n) in surface-controlled electrochemical reactions. Thus,
the number of electron transferred in peak I and peak III in Figure 4.8A was to be 0.8 and 1.0, respectively. The direct glucose electrochemical oxidation reaction on the surface of nitrogen-doped Co₃O₄ nanofibers at peak III (+0.64 V) can be presumably proposed as following equations:

\[ 2\text{CoO}_2 + \text{Glucose} \rightarrow 2\text{CoOOH} + \text{Gluconolactone} \quad (3) \]

Considering the consumption of CoO₂ of glucose and production of CoOOH in eqn. (3), one can conclude that the extent of reaction (2) favor forward direction (CoOOH → CoO₂), thus providing an enhanced glucose oxidation peak III over peak I upon glucose addition (Figure 8A). As a comparison, the cyclic voltammetry responses of Nafion/GCE to the absence and presence of 5 mM of glucose shows no difference, further supporting that glucose oxidation is attributed to NH-Co₃O₄ NFs.

Furthermore, with decreased concentration of sodium hydroxide (pH < 13), the Nafion/NH-Co₃O₄ NFs/GCE electrode lost its glucose catalytic function (data not shown here), demonstrating a critical role of hydroxide ion (OH⁻) in direct glucose oxidation.

As aforementioned that peak III was significantly pronounced than peak I, anodic oxidation peak III at potential 0.64 V (vs. Ag/AgCl) was selected as the applied potential for subsequent amperometric detection of glucose in alkaline solution. As revealed in Figure 4.9B, the non-enzymatic glucose sensor displayed a rapid glucose response within 5 seconds, a good sensitivity of 87.67 µA mM⁻¹ cm⁻² and a detection limit of 0.38 µM (S/N=3). The resulted sensitivity is 2.4-fold higher than our previous report based on electrospun solid Co₃O₄ nanofibers [199]. The increased sensitivity toward glucose in alkaline solution can be attributed to the hollow structure, resulting in much more active sites per unit surface area. The corresponding calibration curve can be fitted using Langmuir isothermal fitting theory [199]. The Langmuir isothermal fitting can be obtained and showed in below:
The as-developed sensor was further employed for the detection of glucose in human serum sample. Figure 8D illustrated the amperometric response to successive additions of human serum and 10 mM glucose solution in the volume of 5 µL and 10 µL. The concentration of glucose in human serum sample was calculated to be 6.50 mM. In addition, a commercial glucose meter (OneTouch UltraMini, LifeScan, Inc. CA) was used to measure the glucose concentration in human serum sample and the detected glucose concentration is 6.00 mM. Our sensing result is in good agreement with that from the commercial glucose sensor, indicating the accuracy of our sensor.

Figure 4.9. (A) The response of CVs of the Nafion/GCE and Nafion/NH-Co$_3$O$_4$ NFs/GCE in the absence (d and b) and presence of 5 mM glucose (c and a), respectively. (B) Amperometric response of the Nafion/NH-Co$_3$O$_4$ NFs/GCE with successive additions of glucose to 0.1 M NaOH
at an applied potential at +0.64 V. Inset: the amperometric response of consecutive addition of 1 µM and 2 µM glucose for three times at each concentration. (C) The corresponding Langmuir isothermal fitting curve (blue line). (D) Amperometric response of Nafion/NH-Co₃O₄ NFs/GCE with successive additions of analytes in the sequence of 5 µL human blood serum sample, 5 µL of 10 mM glucose in PBS buffer, 10 µL blood serum sample, and 10 µL of 10 mM glucose in PBS buffer into 0.1 M NaOH solution (each for 3 times).

To investigate the selectivity of the developed sensor, D-glucose was used for amperometric measurement against uric acid (UA), ascorbic acid [18], and 4-acetaminophen (4-AP). The glucose concentration in healthy human body ranges from 4.4 mM to 6.6 mM, and the endogenous AA and UA is about 0.125 mM and 0.33 mM in blood samples, respectively. Therefore, a healthy level glucose concentration and the endogenous level of UA and AA are tested. In addition, 4-AP is typically lower than 0.1 mM in blood, thus 0.1 mM of 4-AP was used for interference experiments. Figure 4.10 shows the normalized amperometric response of 5 mM D-glucose against 0.125 mM and 0.33 mM of AA and UA as well as 0.1 mM of 4-AP in alkaline solution (0.1 M NaOH). One can see that UA, AA and 4-AP result in insignificant interference. Furthermore, fructose, xylose, galactose, maltose, and sucrose were also employed for selectivity study with their individual concentration to glucose concentration at an aggressive 1 to 10 ratio. The rationale to choose such ratio is due to the fact that the actually physiological concentration of glucose is typically 30-50 folds higher than those of saccharides [151]. As shown in Figure 4.10, the result indicated that other sugars would not interfere glucose detection in real sample detection, which may be attributed to the low physiological concentration of other sugars. It is also indirectly supported by the good agreement between our sensor and commercial glucose sensor for glucose detection in human serum sample.
Figure 4.10. Amperometric response of Nafion/NH-Co$_3$O$_4$ NFs/GCE electrode at an applied potential of +0.64 V to the addition of 5 mM glucose, 0.125 mM AA, 0.33 mM UA, and 0.1 mM 4-acetamnophen. The amperometric response of the sensor at the same potential to the addition of 100 µM glucose and 10 µM fructose, xylose, galactose, maltose, sucrose, respectively. The responses were normalized to combine into one chart.

3.4. Solid-state pH sensing of Nafion/NH-Co$_3$O$_4$ NFs/GCE

The as prepared Nafion/NH-Co$_3$O$_4$ NFs/GCE was investigated for its pH sensing performance in pH titration using universal buffer. Since Garavaglia, R. et al. [279] firstly reported the thermal decomposition of aqueous cobalt nitrate to form Co$_3$O$_4$, cobalt oxide, there only have very few reports about using Co$_3$O$_4$ in solid-state pH detection. The pH sensing mechanism of cobalt oxide typically involves in protonation or deprotonation at the interface of solid-state of nanostructure[303]. Further more, to address the applicability of the as-synthesized Nafion/NH-Co$_3$O$_4$ NFs/GCE as a solid-state pH sensor, pH titration was carried out from pH 3.0 to pH 9.0 and in reverse
titration direction (pH 9.0 to pH 3.0), as well as pH 9.0 to pH 13.0 and vice versa. The pH sensing of a typical solid-state pH sensor is recorded in terms of the electromotive force (EMF) of the modified working electrode versus reference electrode, as shown in Figure 4.11A and 4.11C. By using a commercial pH meter, the actual pH value in solution was readout. In addition, rapid response towards addition of acid and basic solution was observed within 8s before reaching stabilization level, which is superior to the commercial pH meter. As such, the Nernst constants are 12.9 mV/pH (pH titration from 3.0 to 9.0), 15.9 mV/pH (pH titration from 9.0 to 3.0), 6.8 mV/pH (pH titration from 9.0 to 13.0), 10.7 mV/pH (pH titration from 13.0 to 9.0). The difference of the EMF to the same pH level is induced by the hysteresis effect, which could be ascribed to the hydration degree on NH-Co$_3$O$_4$ NFs or the different oxidation states. Sub-Nernst constant was acquired compared with theoretical value of 59 mV/pH at room temperature. It is worth noting that as control experiment the Nafion/GCE only results in a Nernst constant of 5.8 mV/pH and 5.9 mV/pH during pH titration in the pH range from 3.0 to 9.0 and vice versus, respectively, while it has negligible pH sensitivity in pH range of 9-13 (data not shown), indicating that the pH sensitivity of the as-prepared Nafion/NH-Co$_3$O$_4$ NFs/GCE is mainly attributed to the presence of NH-Co$_3$O$_4$ NFs in the range of pH 9.0-13.0. The Nafion membrane holds a synergistic effect with NH-Co$_3$O$_4$ NFs on pH titration sensing. This study further corroborates the claim that the prepared NH-Co$_3$O$_4$ NFs modified sensor can be applied for both glucose and pH detection.
Figure 4.11. The response of Nafion/NH-Co$_3$O$_4$ NFs/GCE to the change of proton concentration adjusted by 1 M HNO$_3$ and 1 M NaOH titration experiment by measuring Electromotive force (EMF) vs. time in the range of pH 3.0 to 9.0 (A) and in the range of pH 9.0 to 13.0 (C) and its corresponding calibration curve, indicating sub-Nernst constant in the range of pH 3.0 to 9.0 (B) and in the range of pH 9.0 to 13.0 (D).

4.4. Conclusion

As a dual functional material, N-doped-hollow-Co$_3$O$_4$ nanofibers NFs were fabricated using core-sheath electrospinning technique followed by annealing process, and then used as the sensing material for glucose and pH sensing in this study. The as-prepared nitrogen-doped hollow cobalt oxide nanofibers were characterized by scanning electron microscopy, transmission electron microscopy, X-ray powder diffraction, and Raman
spectroscopy, while the electrochemical and electrocatalytic performance of the nitrogen-doped hollow $\text{Co}_3\text{O}_4$ NFs based dual sensor toward pH and glucose determination were validated using cyclic voltammetry, amperometry, open circuit potential, respectively. The nitrogen-doped hollow $\text{Co}_3\text{O}_4$ NFs possess sub-Nernst constant at 31.3 mV/pH in the range of pH 3.0 to 9.0 and 41.1 mV/pH in the range of pH 9.0 to 13.0, while it also possesses a sensitivity of 87.67 µA mM$^{-1}$ cm$^{-2}$, a limit of detection of 0.38 µM (S/N=3.3) and a good selectivity against ascorbic acid, uric acid, 4-acetamenophen as well as various kinds of sugars. Its good accuracy toward human serum sample in determining glucose level was validated using commercial glucose meter. All these features indicate that the N-doped $\text{Co}_3\text{O}_4$ NFs are a promising multifunctional sensing material in the development of solid-state pH sensor and non-enzymatic glucose sensor.
Chapter 5

Heterogeneous Iridium Oxide/Au Nanoparticles for Non-Enzymatic Glucose Sensing and pH Probing
Abstract

Both pH-sensitive and glucose-responsive heterogeneous gold-doped iridium oxide nanoparticles (IrO$_2$–Au NPs) were synthesized through electrospinning followed by high-temperature calcination. The as-prepared IrO$_2$–Au NPs were systematically characterized using various advanced techniques including scanning electron microscopy, X-ray powder diffraction and Raman spectroscopy, and then employed as a dual functional nanomaterial to fabricate a dual sensor for both non-enzymatic glucose sensing and solid-state pH monitoring. The sensing performance of the IrO$_2$–Au NPs based dual sensor toward pH and glucose was evaluated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively. The results show that the as-prepared IrO$_2$–Au NPs not only maintain accurate and reversible pH sensitivity of IrO$_2$, but also demonstrate a good electrocatalytic activity of Au toward glucose oxidation in alkaline medium at a low applied potential with a sensitivity of 21.20 µA·mM$^{-1}$·cm$^{-2}$, a limit of detection of 2.93 µM (S/N=3) and a reasonable selectivity against various interferences in non-enzymatic glucose detection. These features indicate that the as-prepared IrO$_2$–Au NPs hold great promise as a dual-functional sensing material in the development of a high-performance sensor for both solid-state pH and non-enzymatic glucose sensing.

Keywords: Gold-doped iridium oxide nanofibers; glucose sensing; pH sensing; alkaline and neutral activity;
5.1 Introduction

In the past decades, pH sensing technology and glucose sensing technology has been separately and extensively studied due to their importance in probing the acidity/alkalinity of aqueous solutions in our daily research and blood glucose level for diabetic patients, respectively. With respect to pH sensing, conventional glass-type pH electrode is the most widely used one in laboratory environment; however, it suffers from the fragileness. To improve the durability of pH sensors, ion-selective field effect transistor[304-307] and optical pH sensors[308] are developed. However, their wider applications are greatly limited by its high power consumption, high cost, and unsuitability for some harsh environment applications. Therefore, solid-state pH sensor measuring the electromotive force difference between the sensing and reference electrodes has gradually attracted the researcher attentions in pH sensing because of its ability for miniaturization, cost-effectiveness, as well as the long-term stability and durability. Up to date, a spectrum of pH-responsive metal oxides have been extensively studied for pH detection [251, 309], some of which hold great promise. On the other hand, intermittent and continuous glucose monitoring is of paramount importance for diabetic patients to track and manage their blood glucose level. Nowadays, glucose oxidase (GOx) and glucose dehydrogenase (GDH) based test strips dominates over 85% of glucose sensor market. Although great success has been achieved using GOx and GDH, the intrinsic thermal and chemical sensitivity of enzyme stimulates the research to pursue more stable non-enzymatic catalysts in glucose detection. Consequently, non-enzymatic glucose sensors are developed as an alternative. Amongst various types of non-enzymatic glucose sensing materials, metal oxides stand out in the development of non-enzymatic glucose sensors because of their easy accessibility, low cost, and superior chemical/thermal stability. A range of metal oxides and their composite materials (e.g. Co$_3$O$_4$[199, 201], Co$_3$O$_4$/graphene[208], NiO[193], noble metal doped NiO[156], CuO[170, 185], Cu$_2$O-TiO$_2$[187], etc.) were exploited as innovative non-enzymatic glucose catalysts in glucose detection.

Although there are numerous reports about solid-state pH sensing or metal oxide based non-enzymatic glucose sensing, the majority of the reports are developed based on the
concept of “one sensor for one target”. The development of dual sensors is heavily overlooked because of the lack of multi-functionality in single sensing material. Therefore, a dual sensor, which can accomplish both non-enzymatic glucose sensing and solid-state pH sensing, still remains unmet challenge. To realize dual sensor concept, novel functional sensing materials or current sensing materials with newly explored functions should be employed in the construction of sensors.

In our previous study [310], iridium oxide has been demonstrated with both good solid-state pH sensing and glucose sensing properties, while noble metals, especially Au[80] and Pt[127], show good conductivity and glucose sensing property. To further improve the sensing performance of iridium oxide, in this study, gold will be doped into iridium oxide during its preparation process. Compared to other conventional metal oxides, one can expect that iridium oxide nanostructured material with gold-doping should not only possess pH sensing property (iridium oxide), but also hold the promise to lower the operating potential in glucose sensing (gold), which are accomplished by taking the advantageous sensing property of iridium oxide and gold, respectively.

The goal of this study aims at developing a dual functional electrochemical sensor for both glucose and pH sensing using a composite sensing material, which consists of IrO₂ and Au. Au-doped IrO₂ nanoparticles (IrO₂-Au NPs) were prepared by electrospinning techniques followed by high temperature annealing process. The as-prepared IrO₂-Au NPs sensing material was employed to modify the glassy carbon electrode. Its pH and glucose sensing performance was systematically investigated using open circuit potential, cyclic voltammetry and amperometric techniques, respectively.

5. 2. Experimental

5.2.1. Reagents

Iridium (IV) tetrachloride was purchased from Alfa Aesar and used without further purification. Polyvinylpyrrolidone (PVP, MW. 1,300,000) and Nafion 117 solution (purum, ~20% in a mixture of lower aliphatic alcohols and water) were supplied from
Sigma-Aldrich. Hydrogen tetrachloroaurate trihydrate (HAuCl₄·3H₂O) Dimethylformamide (DMF), D-(-)-glucose, 4-acetaminophen, ascorbic acid, and uric acid, as well as ethanol were obtained from Acros Organics. 10 mM pH 7.4 PBS buffer contained 137 mM NaCl, 2.7 mM KCl, 10 mM Na₂HPO₄, and 1.8mM KH₂PO₄. All aqueous solutions were prepared with deionized water (18.2MΩ cm) generated by a Barnstead water system.

5.2.2 Fabrication of IrO₂-Au nanoparticles

0.19 g iridium tetrachloride was dissolved in 4 mL of dimethylformamide (DMF) solution, followed by the addition of 0.1 g HAuCl₄ and another 0.87 g PVP. The mixed solution was under magnetic stirring for overnight. The as-prepared homogenous solution was then electrospun using 23-gauge needle with a flow rate of 0.3 mL/h at an applied voltage of 20 kV over an aluminum foil collector (15 cm to the tip of needle). On the other hand, 0.19 g iridium tetrachloride was dissolved in 4 mL of dimethylformamide (DMF) solution, followed by 0.87 g of PVP (M.W. 1,300,000). The mixed solution was also stirred overnight before electrospinning. Such precursor solution without the addition of HAuCl₄ or IrCl₄ was also prepared for control purpose in characterization. The IrCl₄·HAuCl₄/PVP and IrCl₄/PVP nanofibers collected on the collector were then peeled off. After 3 h dehydration process at 80 °C in an oven, the as-prepared precursory IrCl₄·HAuCl₄/PVP or IrCl₄/PVP nanofibers were calcined under ambient atmosphere at 900 °C for 3 h with a ramp-up speed at 2°C/min. The furnace was then allowed to naturally cool down to room temperature and the annealed IrO₂-Au NPs and IrO₂ NFs were collected.

5.2.3. Preparation of IrO₂-Au NPs modified glassy carbon electrode

Before modification of the surface, glassy carbon electrode (GCE, dia. 3 mm) was polished with 1µm and 0.05 µm alumina slurries sequentially, and then rinsed with DI water. Afterwards, the electrode was cleaned by ultra-sonic bath for 5 minutes in acetone, ethanol and DI water sequentially, and then dried at room temperature. The loading of iridium oxide/Au NPs on the glassy carbon electrode was first optimized through comparing anodic peak current at +0.67 V (vs. Ag/AgCl) of cyclic voltammetry in 0.1 M NaOH, and peak current at +0.3 V (vs. Ag/AgCl) in 0.1 M PBS buffer.
As shown in Figure 5.1, 7 mg/mL of stock solution with a fixed loading volume of 8 µL is the optimal concentration, which was used for subsequent experiments. To prepare 7 mg/mL IrO$_2$-Au NPs suspension, 7 mg of calcined IrO$_2$-Au sample was suspended in 1.0 ml ethanol and then subject to 30 min of ultra-sonication. Afterwards, 8 µL IrO$_2$-Au NPs/ethanol suspension was drop-cast onto pre-cleaned glassy carbon electrodes. After solvent evaporation, 5 µL of Nafion solution (1wt% in ethanol) was further cast onto the top of IrO$_2$-Au NPs and dried in air to entrap the nanoparticles. The as-prepared electrode is denoted as Nafion/IrO$_2$-Au NPs/GCE. Nafion-coated glassy carbon electrodes (Nafion/GCE) were also prepared as the control electrode following the same procedure. Before use, each electrode was submerged into DI water for an appropriate time to allow Nafion membrane to swell. All experiments were repeated at least 3 times to ensure the reproducibility.

5.2.4. Apparatus and electrochemical measurements

A JEOL 6335F field-emission scanning electron microscope (SEM) was used to examine the morphology and the size of the as-electrospun precursory nanofibers and iridium (IV) oxide/Au NPs. The X-ray powder diffraction patterns (XRD) were obtained with a Rigaku UltimaIV instrument with Cu Kα radiation ($\lambda=0.154056$ nm) operating at 40 kV and 45 mA beam current. Raman spectra were recorded at ambient temperature on a
Reinshaw Ramanscope Micro-Raman with 514 nm wavelength lasers. Cyclic voltammetry (CV), amperometry and open circuit potential potential measurements were performed on a CHI 601C Electrochemical Workstation (CH Instruments, USA). All experiments were conducted using a standard three-electrode electrochemical cell, consisting of a working electrode (GCE, dia. 3 mm), an Ag/AgCl reference electrode, and a platinum counter electrode (dia. 3 mm). For amperometric glucose detection, all signals were recorded after current decayed to a steady-state value and a stirrer was used to provide convective mixing. For pH sensing, the pH-adjustable buffer was prepared using a recipe from a previous report[248]. Briefly, pH 3.0-9.0 solutions were universal buffers containing 10 mM potassium hydrogen phthalate, 10 mM phosphate, and 10 mM Tris, while pH 10.0 and 11.0 solutions contained 50 mM sodium carbonate and 10 mM borax and 140 mM of NaCl. The pH adjustment was realized by addition of 1 M HNO₃ or 1 M NaOH.

5.3. Results and discussion

5.3.1 Morphology and composition of IrO₂-Au NFs

Figure 5.2A showed the typical morphology of the precursory IrCl₄-HAuCl₄/PVP nanofibers. One can see that the precursory nanofibers possessed smooth surface and the diameter of the precursory nanofibers is 129.50 ± 22.58 nm (IrCl₄/HAuCl₄/PVP nanofibers). After the degradation of PVP and decomposition of IrCl₄ and HAuCl₄ at high temperature, the nanofiber morphology disappeared (Figure 5.2B) due to the migration of iridium oxide and Au element. Such observation was also supported by TEM imaging (Figure 5.3).
In order to monitor the composition change of IrCl₄/HAuCl₄/PVP precursor before and after annealing process, Fourier-Transform Infrared spectroscopy (FT-IR) was applied to analyze the samples. One can see that the transmission bands associated with PVP at ca. 1640 cm⁻¹, 1420 cm⁻¹, and 1290 cm⁻¹ disappeared after calcination, shown in Figure 5.4, indicating complete degradation of PVP.
To investigate phase purity of the as-synthesized gold-doped IrO$_2$ nanoparticles, IrO$_2$ nanofibers, and gold particles, X-ray powder diffraction was applied for analysis and the results were presented in Figure 5.5. The reflections at 2\(\theta\)=38.09°, 44.29°, 64.50°, 77.49°, 81.68° were measured and recorded in the calcined Au particles, and they were fit into the miller index of (111), (200), (220), (311), and (222) (JCPDS Card File No. 03-065-2870). The reflections at 2\(\theta\)=27.85°, 34.51°, 39.80°, 40.44°, 53.79°, 57.77°, 58.21°, 65.39°, 65.91°, 69.06°, and 73.14° were detected in the as-prepared IrO$_2$ NFs. All peaks fit well with IrO$_2$ (110), (101), (200), (111), (211), (220), (002), (310), (112), (301), and (202) (JCPDS Card File No. 15-0870), which indicate the typical cubic fluorite-like structure of IrO$_2$. 

**Figure 5.4** The Fourier-transform infrared spectroscopy (FT-IR) of calcined IrO$_2$-Au and Au powder.
Figure 5.5 The X-ray powder diffraction (XRD) analyses of Au (blue line), IrO$_2$ (red line), and IrO$_2$-Au (black line) from calcined HAuCl$_4$/PVP, IrCl$_4$/PVP, and IrCl$_4$/HAuCl$_4$/PVP precursory nanofibers.

Typical Raman spectra of the as-prepared IrO$_2$-Au NPs and the precursory IrCl$_4$/HAuCl$_4$/PVP nanofibers are shown in Figure 5.6. There is no obvious peak observed for precursory nanofibers. However, there are three major peaks at 550, 718 and 743 cm$^{-1}$ for the IrO$_2$-Au NPs. Those peaks can be assigned to E$_g$, B$_{2g}$ and A$_{1g}$ modes of the crystalline IrO$_2$, further indicating the formation of IrO$_2$. Moreover, no carbon trace was observed in calcined IrO$_2$–Au NPs, which was corroborated by the lack of carbon’s G-band at ~1600 cm$^{-1}$.
Figure 5.6 The Raman spectroscopy of calcined IrO$_2$-Au nanofibers labeled with line (a) and precursory IrCl$_4$/HAuCl$_4$/PVP nanofibers labeled in line (b), respectively.

5.3.2. Electrochemical behavior of the IrO$_2$-Au NPs modified GCE (Nafion/IrO$_2$-Au NPs/GCE) toward both glucose and pH monitoring

5.3.2.1. Glucose sensing

Being attacked by hydroxide ions, iridium oxide has been reported to form different oxidation valences, thus endowing the electrochemical redox capability. In this study, 0.1 M NaOH and 0.1 M PBS buffer were used as electrolytes to scrutinize the performance of the as-prepared Nafion/IrO$_2$-Au NPs/GCE for non-enzymatic glucose sensing. The CVs (scanning from -0.5 V to +0.8 V vs. Ag/AgCl) of the Nafion/GCE (Figure 5.7A) and Nafion/IrO$_2$-Au NFs/GCE in the absence and presence of 5 mM and 10 mM of glucose were first investigated in alkaline solution (0.1 M NaOH) and 0.1 M PBS buffer, respectively. In the absence of glucose, there was no obvious peak observed on the Nafion/GCE, indicating negligible catalytic character towards glucose. The one for the Nafion/IrO$_2$-Au NPs/GCE showed both typical characteristic for a gold electrode (gold oxide formation and reduction) and a typical characteristic for an iridium oxide electrode (iridium oxidation (IV to VI) and reduction (VI to IV)) in the electrolyte of 0.1 M NaOH.
The result was in a good agreement with literature reports for gold [70, 72, 74, 76, 78, 81, 82, 88, 311, 312] or iridium oxide [310]. Therefore, IrO$_2$-Au NPs in Nafion/IrO$_2$-Au NPs/GCE was responsible for the indication of glucose oxidation in alkaline environment. With the increase of glucose concentration, the peak current at ca. +0.05 V increased accordingly and far more prominent than the characteristic peak of iridium oxide at ca. +0.67 V. Therefore, we chose to measure the glucose concentration by using the characteristic peak of gold in terms of its low operational potential and more pronounced response towards glucose. On the contrary, in the neutral solution of 0.1 M PBS, the responses of both Nafion/GCE and Nafion/IrO$_2$-Au NPs/GCE towards absence and presence of glucose did not show obvious difference, as shown in Figure 5.7B. Therefore, glucose sensing was pursued only in alkaline environment.

![Cyclic voltammetry response](image)

**Figure 5.7 (A)** Cyclic voltammetry response of absence of glucose of Nafion/GCE and Nafion/IrO$_2$-Au NPs/GCE, and in the presence of elevated glucose concentration 5 mM, 10 mM on Nafion/IrO$_2$-Au NFs/GCE modified electrode in 0.1 M NaOH electrolyte. **(B)** Cyclic voltammetry response of absence of glucose of Nafion/GCE, Nafion/IrO$_2$-Au NPs/GCE modified electrodes and presence of elevated glucose concentration 5 mM, 10 mM on Nafion/IrO$_2$-Au NPs/GCE modified electrode in 0.1 M PBS buffer.

Furthermore, Figure 5.8 demonstrates the effect of scan rate on the oxidation and reduction peak currents in the electrolyte of 0.1 M NaOH and 0.1 M PBS buffer,
respectively. One can observe that the oxidation and reduction peak currents linearly increased with the scan rate from 10 mV/s to 200 mV/s (Figure 5.8B and 5.8D), indicating a surface-controlled electrochemical process for Nafion/IrO$_2$-Au NPs/GCE in both electrolytes.

![Cyclic voltammetry response of Nafion/IrO$_2$-Au NPs/GCE](image)

**Figure 5.8** Cyclic voltammetry response of Nafion/IrO$_2$-Au NPs/GCE in the absence of glucose at different scanning rate of 10 mV/s, 20 mV/s, 40 mV/s, 60 mV/s, 80 mV/s, 100 mV/s, 150 mV/s, 200 mV/s in 0.1 M NaOH electrolyte (A) and 0.1 M PBS buffer (C), and their corresponding peak current vs. scan rate linear fit for 0.1 M NaOH (B) and 0.1 M PBS (D).

As the oxidation peak current of Nafion/IrO$_2$-Au NPs/GCE at ca. +0.05 V in 0.1 M NaOH increases proportionally with glucose concentration, amperometric glucose detection using Nafion/IrO$_2$-Au NPs/GCE was conducted at an applied potential of +0.05
V (vs. Ag/AgCl) in the electrolyte of 0.1 M NaOH. Figure 5.9A showed the typical amperometric responses of the developed sensor to successive injection of glucose in 0.1 M NaOH solution. A well-defined, stable and fast amperometric response within 5 s can be observed on the Nafion/IrO$_2$-Au NPs/GCE. With the successive addition of glucose, the Nafion/IrO$_2$-Au NPs/GCE generated a stepwise amperometric response. The corresponding calibration curve of the current vs. glucose concentration was plotted and presented as Figure 5.9B. The electrochemical oxidation of glucose on IrO$_2$–Au NPs is a surface catalytic reaction, which is typically well described by Langmuir isothermal theory in our previous study[199]. Therefore, Langmuir isothermal theory was adopted to fit the calibration curve (Figure 9B) with good fitting results with a correlation coefficient of 0.999.

$$I(\mu A) = \frac{1.498 C_{glucose}(mM)}{1 + 0.329 C_{glucose}(mM)}$$

According to the surface area of GCE, the sensitivity and the limit of detection (S/N=3) were calculated to be 21.20 µA mM$^{-1}$ cm$^{-2}$ and 2.93 µM, respectively.

As a comparison, amperometric glucose detection was also investigated using the characteristic operating potential of IrO$_2$ at +0.67 V (vs. Ag/AgCl). Figure 9C shows the stepwise i-t curve upon successive addition of elevated glucose concentration, while the inset reveals the amperometric response to the addition of low glucose concentration. Following Langmuir-isothermal fitting, the corresponding calibration curve was displayed in Figure 5.9D. The sensitivity and the detection of limit (S/N=3) were calculated to be 8.10 µA mM$^{-1}$ cm$^{-2}$ and 5.13 µM. These results indicate that the detection of glucose at the characteristic peak of Au in IrO$_2$-Au NPs is superior to the one of IrO$_2$. 

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Figure 5.9 Typical Amperometric response of Nafion/IrO$_2$-Au NPs/GCE electrode toward elevated glucose concentration in the electrolyte of 0.1 M NaOH at 0.05 V (vs. Ag/AgCl) (A) and 0.67 V (C) and corresponding Langmuir isothermal fitting (B) and (D).

5.3.2.2. Selectivity of Nafion/IrO$_2$-Au NPs/GCE

The selectivity of the Nafion/IrO$_2$-Au NPs/GCE in pH 13.0 was also investigated against normally co-existed interfering species with glucose such as fructose, xylose, lactose, galactose, maltose, sucrose, dopamine (DA), ascorbic acid (AA), 4-acetoaminophen (4-AP) and uric acid (UA). As the concentration of glucose in blood is typically at least 10-fold higher than those of common interferences[217, 218], the amperometric signal of 100 $\mu$M glucose on the Nafion/IrO$_2$-Au NPs/GCE were compared with those of 10 $\mu$M fructose, xylose, lactose, galactose, maltose, sucrose, 4-AP, UA, and AA. Wang, J. et al. [151] also reported the similar selectivity test for the glucose concentration towards
interferences. Figure 5.10A shows the current vs. time curve of the Nafion/IrO$_2$–Au NPs/GCE toward the sequential injection of glucose and interfering sugars in the electrolyte of 0.1 M NaOH. In addition, the normalized signal of 4-AP, UA, and AA compared with glucose is shown in Figure 10B. Except that xylose, galactose and ascorbic acid results in a minor response, the interference from fructose, lactose, maltose, sucrose, 4-AP and UA was negligible, indicating good selectivity of the developed non-enzymatic glucose sensor.

![Figure 5.10 Amperometric response of Nafion/IrO$_2$-Au NPs/GCE towards 100 µM of D(+)glucose, and 10 µM of D(-)-Fructose, D(+)-xylose, α-lactose, D(+)-galactose, D(+)-maltose, sucrose, ascorbic acid, 4-acetamenophen, and uric acid, revealed in real-time amperometric response (A) and in normalized signal shown in column chart (B).](image)

5.3.3. pH sensing using the Nafion/IrO$_2$–Au NPs/GCE

In aqueous condition, by recording electromotive force (EMF) in varied pH buffer, Nernst-constant can be calculated using a calibrated curve. Iridium oxide has stood out from various kinds of materials due to its high pH sensitivity. As early as in 1989, Yamanka et al. [277] reported both anodically oxidized iridium oxide (AOIRF) and cathodically oxidized iridium oxide (COIRF). Since then, iridium oxide has been extensively exploited in solid-state pH sensing. Typically, the redox intercalation equilibrium can be found in different oxidation states of IrO$_x$, which is attributed to its pH sensing mechanism[265, 313-315]. To test the pH sensitivity of the developed
Nafion/IrO2-Au NPs/GCE, pH titration experiments were conducted in different pH ranges. As a comparison, a commercial pH meter was used to record the pH variation in the same solution simultaneously. The corresponding EMF value was recorded in real-time format and shown in Figure 5.11 A and 11C. One can observe that the Nafion/IrO2-Au NPs/GCE responded to pH variation rapidly and the relative stable potential were typically acquired within 10 seconds, which is comparable with the stabilizing time for commercial pH meter. The calculated Nernst constants are 27.50 mV/pH (titration from pH 3 to pH 9), 34.40 mV/pH (titration from pH 9 to pH 3), 47.70 mV/pH (titration from pH 9 to pH 12) and 52.40 mV/pH (titration from pH 12 to pH 9). Hysteresis was observed during titration experiment, which can be reflected on the deviation of the open circuit potential for the same pH value. It could be ascribed to several factors, including different thermodynamic equilibrium formed at the same pH value, different hydration degree of gold-doped iridium oxide nanoparticles, etc. It showed sub-Nernst constant at room temperature (25 °C) compared with the theoretical value of 59 mV. For the clarification of the Nafion membrane effect in pH titration experiment, Nafion/GCE was carried out with the same procedures. The corresponding Nernst constants are 5.8 mV/pH and 5.9 mV/pH during titration in the range of pH 3 to 9 and pH 9 to 3, respectively, and negligible sensitivity towards pH change in pH 9 to 12 and pH 12 to 9 (data not shown), which indicate that the effect of Nafion on pH sensing of Nafion/IrO2-Au NPs/GCE is very minor.
Figure 5.11 Nafion/IrO$_2$-Au NPs/GCE pH titration in the range of pH 3.0 to 9.0 (A) and pH 9.0 to 13.0 (C) and corresponding linear fit shown in (B) and (D).

5.4. Conclusions
In summary, a novel dual electrochemical sensor based on IrO$_2$-Au NPs modified glassy carbon electrode was developed. Due to the pH sensitivity of iridium oxide and glucose oxidation capability of Au in IrO$_2$-Au NPs, the developed sensor was applied for both non-enzymatic glucose sensing in alkaline environment and pH monitoring. The experiment results show that the IrO$_2$ is responsible for the observed pH sensing capability, while Au is attributed to glucose detection at a low applied potential in alkaline environment. All these features indicate that the high-temperature annealed IrO$_2$-Au NPs are a promising multifunctional sensing material in the development of an integrated solid-state pH sensor and non-enzymatic glucose sensor.
Chapter 6

Summary, Future Prospects and Challenges

6.1 Summary

On the one hand, the good accuracy of glucose measurements concerns in the groups of diabetes patients for insulin injections. On the other hand, pH sensing matters in the large varieties of practical application such as water quality control, laboratory buffer preparations, etc. Being able to monitor the pH of liquid along with the glucose determination leads to more accurate and reliable readout of the level of blood glucose. Up to date, there are limited literature reports regarding dual functional materials for both glucose measurements and pH sensing for improved managements of glucose level in blood. Therefore, this Ph.D. project aims to develop such kind of materials that hold the glucose determination and pH sensing property at the same time.

Chapter 2 discussed the sensing mechanisms of glucose based on enzymatic and non-enzymatic platform, as well as several kinds of pH sensor that currently used. The projects hypothesis and motivations were introduced the Chapter 1 as well. By applying electrospinning and annealing process, in Chapter 2, iridium oxide nanofibers were synthesized and characterised by morphological characterizations and surface characterizations, indicating that the as-synthesized iridium oxide in the form of IrO$_2$. Furthermore, electrochemical characterizations based on glassy carbon electrodes demonstrated sensitive and selective property of iridium oxide toward glucose sensing and near-Nernst constant pH sensing property on both bulky electrode and screen-printed electrodes. The pH sensitivity locates in the range of pH 3.0 to pH 12.0. In addition, it holds capability to probe the alkalinity of 0.1 M NaOH solution, reflecting flexible capability to sense extreme basic solution.

Chapter 3 explored the rhodium oxide nanocorals sensing property toward glucose and pH. As-fabricated rhodium oxide nanocorals material holds the form of beta-Rh$_2$O$_3$,
indicated by X-ray powder diffraction analysis. Following similar study methods, it shows relatively good sensitivity and good selectivity among ascorbic acid, uric acid, 4-acetaminophen and negligible interference from dopamine. The amperometric studies also revealed good long-term stability results for the modified glassy carbon electrode. Open circuit potential was applied for the investigation of pH sensing of rhodium oxide, resulting in sub-Nernst constant in the range of pH 3.0 to pH 13.0.

Chapter 4 revisited the previously studied cobalt oxide nanofibers, but in different structure (i.e. core-shell cobalt oxide nanofibers), holding both improved glucose sensitivity and sub-Nernst constant of pH sensitivity. The core-shell structure of cobalt oxide was also synthesized by feasible electrospun-annealing step and applied for glucose sensing and pH sensing test. Transmission electron microscopy was utilized for the characterization of core-shell structure of cobalt oxide nanofibers. X-ray powder diffraction was used for the analysis of cobalt oxide as in the form of Co$_3$O$_4$. In addition, Raman spectroscopy, and X-ray Photoelectron Spectroscopy (XPS) were also used for the investigation of core-shell cobalt oxides. Open circuit potential was applied for the pH responsive test. The results show that core-shell cobalt oxide modified glassy carbon hold sub-Nernst constant in the pH range of 3.0-13.0.

Chapter 5 built a novel dual electrochemical sensor based on IrO$_2$-Au NPs modified glassy carbon electrode. Due to the pH sensitivity of iridium oxide and glucose oxidation capability of Au in IrO$_2$-Au NPs, the developed sensor was applied for both non-enzymatic glucose sensing in alkaline environment and pH monitoring. The experiment results show that the IrO$_2$ is responsible for the observed pH sensing capability, while Au is attributed to glucose detection at a low applied potential in alkaline environment. All these features indicate that the high-temperature annealed IrO$_2$-Au NPs are a promising multifunctional sensing material in the development of an integrated solid-state pH sensor and non-enzymatic glucose sensor.
6.2 Future prospects and Challenge

Metal oxides have been extensively studied in alkaline environments for non-enzymatic glucose sensing with improved sensitivity and selectivity. Few metal oxides such as ferric oxide have proved with ability to catalyze glucose in neutral pH, which holds great promise for future implantable glucose sensing application. Furthermore, UV light was also employed to endow metal oxides such as zinc oxide with the capability to mimic enzyme for glucose oxidation in neutral pH. Up to date, a great deal of efforts has been taken to improve the sensitivity and the limit of detection without losing too much specificity in metal oxide based non-enzymatic glucose sensing. To improve the sensing performance of metal oxides, various functional materials such as conducting polymer and carbon materials (e.g., graphene, graphene oxide, reduced graphene oxide, etc.) were incorporated with metal oxides to take the synergistic effect among different materials for enhanced glucose sensing. Considering the clinical requirement in glucose detection, both sensitivity and detection of limit of current metal oxide based non-enzymatic glucose sensors can satisfy such requirement. However, the specificity of these oxides in glucose sensing was not significantly researched and improved against a number of interferences such as dopamine, 4-acetamenophen, ascorbic acid, uric acid, fructose, galactose, xylose, maltose, sucrose, etc. In order to be as selective as enzyme based glucose sensors, future researchers have to develop a strategy to overcome the intrinsic poor selectivity of metal oxides.

In addition, comparing with intermittent tracking of blood glucose level, continuous glucose sensing has been regarded as the dominating glucose monitoring method in the near future. It is envisioned by some researchers that implantable monitoring products will replace all glucose sensors on the market by the year of 2023. However, most of the current continuous glucose monitoring products on the market is dependent on the specific catalytic property of either glucose oxidase or glucose dehydrogenase. To employ metal oxides for in vivo glucose monitoring, there are two basic requirements. First, the biocompatibility of metal oxides should be evaluated and some biocompatibility study using animal model should be carried out. Second, it remains a challenge for metal oxides to serve as catalysts for direct glucose oxidation in neutral pH environment with
high selectivity. Currently, only ferric oxide and FeOOH, as well as Au [79, 80, 312, 316] and Pt [41, 73, 121, 123, 125-128, 131, 317], possess such catalytic activity toward non-enzymatic glucose detection in neutral pH. Ferric oxide, for example, has the potential for continuous glucose monitoring in neutral pH, however, its selectivity for glucose against other compounds should be systematically investigated and improved in order to be as competitive as enzyme based glucose biocatalysts. For all other metal oxides, which must work in the alkaline solution, an innovative doping strategy should be adapted to reduce the operating pH down to neutral. To achieve this goal, the collaboration between sensor engineer and material scientist is required. With the development of computation tools in correlating materials composition and morphology to their property and function, we expect this goal can be realized in the near future.
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Appendix A Biography

Qiuchen Dong was raised up from August 17th 1990 in the city Taiyuan, Shanxi Province, China. He received B.E degree in Bioengineering in Shenyang University of Chemical and Technology (The school name was changed in the year of 2012 from Shenyang Institute of Chemical and Technology to the current one), Shenyang, China in June 2013. In August 2013, Qiuchen was admitted to the Department of Biomedical Engineering, University of Connecticut, Storrs, where he will obtain his Ph.D. in Biomedical Engineering in August 2018.

Journal Publications and Conference Presentations

3. Qiuchen Dong, Xudong Wang, William Willis, Donghui Song, Yikun Huang, Baikun Li, Jing Zhao, Yu Lei. "Nitrogen-doped core-shell Co$_3$O$_4$ nanofibers for both improved non-enzymatic glucose sensing and solid-state pH sensing". Electroanalysis. Accepted.
Conference Presentations


2. Qiuchen Dong, Yikun Huang, Donghui Song, Huixiang Wu, Fei Cao, Yu Lei. Dual functional rhodium oxide nanocorals enabled sensor for both non-enzymatic glucose and solid-state pH sensing. 27th Connecticut Symposium on Microelectronics & Optoelectronics (CMOC), Orange, CT, USA. April 4, 2018. (Presentation)

3. Qiuchen Dong, Donghui Song, Yikun Huang, Yu Lei. Dual functional rhodium oxide nanofibers for both non-enzymatic glucose sensing and pH sensing. 4th Annual Engineering Poster Competition, University of Connecticut, Storrs, CT, USA. March, 2018. (Poster)