

Nanomaterials for electrochemical non-enzymatic glucose biosensors

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This review overviews the recent development of nanomaterials for the application of electrochemical non-enzymatic glucose biosensors. The electrocatalytic mechanism and glucose sensing performance of a variety of nanostructured materials including metallic nanoparticles, metal oxides, metal complexes, alloys and carbon nanomaterials are discussed. The merits and shortfalls of each nanomaterial as electrocatalyst for non-enzymatic biosensing are evaluated and the prospects of non-enzymatic glucose biosensors are presented.

1 Introduction

Diabetes is a condition marked by the inability of the body to properly manage the level of glucose in the blood. In type 1 diabetes, the body does not make insulin, the hormone that regulates the usage of sugar in a human body. Individuals with type 1 diabetes rely on the regular monitoring of blood glucose concentration and intermittent injection of insulin to keep their blood sugar level normal. The blood glucose test is usually conducted by the patients themselves at home by

pricking their fingers several times in a day to collect blood, which is then dropped on a test strip. Without strict control of glucose, type 1 diabetic individuals suffer from serious and chronic complications, such as blindness and tissue damage. Type 2 diabetes mellitus results from insulin resistance and relative deficiency of insulin secretion. Constituting 90% of the diabetes cases, type 2 diabetics may suffer from complications such as heart disease, stroke and kidney failure. Therefore, routine measurement of blood sugar level is also necessary for type 2 diabetics.

The glucose biosensor developed rapidly since its invention 50 years ago, and currently occupies approximately 85% of the entire biosensor market. Besides blood glucose measurement, glucose biosensors are also widely used in bioindustrial process monitoring, quality control and fuel cells. Although

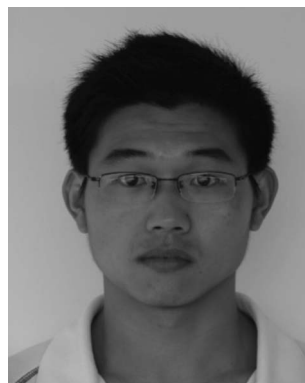
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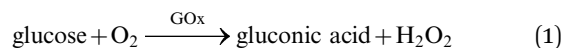
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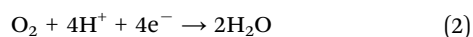
commercially available glucose sensing devices are dominated by enzymatic systems, the last decade has seen an increasing research interest in non-enzymatic glucose sensors, especially those based on nanomaterials. The emerging nanotechnology has brought new opportunities and inspirations for the development of innovative non-enzymatic glucose sensors. The nanostructured electrocatalysts promise to solve the problems associated with non-enzymatic electrode such as poor selectivity and surface fouling, and nanomaterials based non-enzymatic biosensors show significantly higher sensitivity than enzymatic systems. Two comprehensive reviews on electrochemical non-enzymatic glucose sensors have been published by Park *et al.*¹ and Toghiani *et al.*² in 2005 and 2010, respectively. We feel the necessity to write this review because the recent two years has seen the number of publications on nanomaterials based non-enzymatic glucose sensors increasing at a considerable rate. There are several excellent reviews on electrochemical enzymatic glucose biosensors reported by Wang^{3,4} and Heller *et al.*,⁵ therefore, we just briefly discussed the history of enzymatic systems herein.

1.1 Brief history of enzymatic glucose biosensor

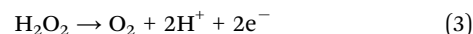
The first-generation glucose sensors were pioneered by Clark and Lyons in the 1950s and 1960s.⁶ Their devices relied on a thin layer of glucose oxidase (GOx) enzyme, immobilized over an oxygen electrode (*via* a semipermeable dialysis membrane), and monitored the amount of oxygen consumed by the enzyme-catalyzed reaction by electrochemical method.⁷ The reaction could be explained by the following equation:



A negative potential was applied to the platinum cathode for a reductive detection of the oxygen consumption:

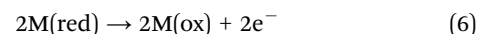
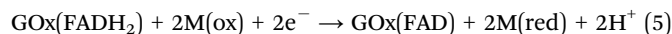


The technique was further developed by Updike and Hicks,⁸ who employed additional oxygen working electrode (without enzyme) and measured the differential current between two working electrodes to correct for the oxygen background variation in samples. Subsequently, Guilbault and Lubrano⁹ introduced another enzyme electrode for blood glucose measurement based on amperometric monitoring of the hydrogen peroxide as a product:

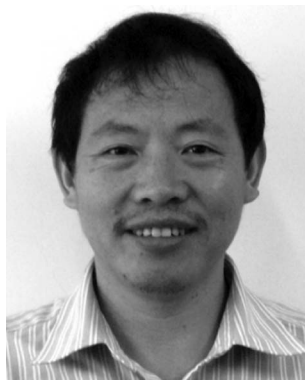


The drawbacks of first-generation glucose sensor are strong dependence of ambient oxygen and too high applied potentials for reduction of oxygen or oxidation of H₂O₂. Both the high negative and positive potentials may cause serious interfering reactions of electroactive compounds (*e.g.*, ascorbate, urate and paracetamol) in the blood if a size-selective membrane is not present.

The second-generation glucose sensors are based on mediators and have been introduced in 1980s.^{10,11} Mediators are small, soluble redox active molecules (*e.g.*, ferrocene derivatives, ferrocyanide, conducting organic salts and quinones) capable of undergoing rapid and reversible redox reactions, shuttling the electrons between the redox center at the active site of enzyme and the electrode surface. The mechanism of the second-generation biosensors could be understood by the following equations:



where M(ox) and M(red) are the oxidized and reduced forms of the mediator. Mediators have replaced O₂ molecules as the electron shuttle to react with the redox active center of enzyme eqn (5) and M(red) are re-oxidized at relatively low potentials which generates a current when they come in contact with the working electrode eqn (6). Incorporation of mediators in



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glucose sensor alleviates the influence of interferential molecules and eliminates the dependence of oxygen for glucose sensing. Taking advantages of high specificity and reliability of second-generation glucose sensors, the first personal glucose meter was commercialized by Medisense Inc. in 1987.⁴ Other companies including Roche Diagnostics, LifeScan, Abbott and Bayer thereafter have launched different types of glucose sensors with lower sample loading volumes and more advanced functions, but the basic concept of glucose sensor design has remained largely unchanged. Although the practicability of second-generation glucose biosensor has been successfully achieved by the commercialization of a series of home-use, disposable devices based on screen printed strips, the soluble nature of most mediators leads to short operation time and irreproducible results, and the potential biotoxicity of mediators prevent the second-generation biosensor from application for *in vivo* glucose testing.

The ultimate goal of glucose sensing is to eliminate the usage of a mediator, even enzyme to lower the fabrication cost and complexity while increasing the durability of the glucose sensor. The third-generation glucose sensor enables direct electron transfer between the redox center of enzyme and electrode, leading to a very high sensitivity and reproducibility without using mediators. The system could be operated a low potential which is close to the physiological enzyme redox potential of ~ 0.44 V.¹² The mechanism of the third-generation of glucose biosensors can be explained by the following reactions:^{13,14}



Due to a significantly lowered operating potential, the interferential responses of electroactive species are also greatly diminished. The third-generation glucose sensor is well suited for the *in vivo* monitoring of blood sugar due to its stability and biocompatibility. However, it suffers from relatively smaller linear range compared to the first-and second-generation glucose sensors. Therefore, the implantable glucose monitors on the market currently are still based on the concept of the first-generation ones. Further effort is needed to improve the performance of the third-generation of glucose sensors in order to meet the commercialization criterion.

1.2 Advantages of glucose sensing without enzyme

The enzymatic glucose biosensor has dominated the glucose sensor industry for more than 20 years. However, a number of critical drawbacks hinder its further development. In the first place, the enzyme-based glucose biosensor suffers from serious stability issues due to the intrinsic nature of protein. Although GOx is more stable than other enzymes, it is still constrained to pH range from 2 to 8, temperature below 44 °C and ambient humidity levels. In addition, GOx can be deactivated by a variety of detergents. In the presence of sodium *n*-dodecyl sulfate at low pH and hexadecyltrimethylammonium bromide at high pH, GOx quickly loses its activity.^{15,16} The thermal and chemical instability of GOx

prevents the enzymatic biosensor from continuously monitoring fermentation process or in human bodies which requires sterilization. Ensuring the stability of enzymatic glucose biosensor requires considerate attention, with a variety of elaborate fabrication strategies including electropolymerization of enzyme within a polymer,¹⁶ covalent cross-linking of enzyme at a pre-treated electrode surface,¹⁷ sol-gel entrapment of enzyme,¹⁸ electrochemical 'wiring' of GOx to mediated polymer chains,¹⁹ *etc.* These efforts ensure the short-term stability of enzymatic glucose biosensor and enable it for single-time disposable usage. Despite the aforementioned contributions having alleviated the problem of enzyme-based electrodes to a certain extent, the glucose sensor based on GOx is easily exposed to harsh thermal and chemical conditions during fabrication, storage and usage. In addition, as diabetes continues to rise in the developing countries, the glucose biosensor with a high fabrication cost and short shelf-life become less viable. All those explain why enzymeless glucose biosensors attract tremendous research interest.

1.3 Mechanisms of non-enzymatic electrooxidation of glucose

Non-enzymatic glucose biosensors are based on the glucose oxidation reaction catalysed by a variety of electrocatalysts, including metals (Au, Pt, Pd, *etc.*), metal oxides (Co₃O₄, CuO, RuO₂, *etc.*), alloys (PtPb, PtRu, *etc.*), complexes (cobalt phthalocyanine tetrasulfonate, nickel hexacyanoferrate, *etc.*) and carbon (carbon nanotubes, boron doped diamond, *etc.*). Except for the last category, all other catalysts listed above contain a transition metal center. There are generally two widely accepted theories that explain the electrooxidation of glucose by transition-metal containing electrocatalysts. Pletcher²⁰ proposed activated chemisorption model which suggested that the electrocatalytic oxidation of glucose occurs *via* a concentrated step, *i.e.*, the adsorption of glucose molecule on the surface of metal-containing electrocatalyst followed by the abstraction of hemiacetalic hydrogen atom. The adsorption process presumably involves the formation of suitable bonds between the adsorbate and the transition-metal substrate with d-electrons and d-orbitals. The hydrogen removal process is deemed as the rate-determining step in most glucose electrooxidation experiments, and is generally considered to occur simultaneously with the chemisorption of analytes. Hence, the adjacent metal active center is occupied by a single adsorbate each time, implying well-spaced adsorption sites on the surface of electrocatalysts with suitable geometry could contribute to the kinetic enhancement of glucose oxidation process. Another model, namely 'Incipient Hydrous Oxide Adatom Mediator' (IHOAM) proposed by Burke,²¹ which involved discussing the role of hydroxyl radicals in the electrocatalytic process. IHOAM was based on the observation that 'active' metal surface atoms undergo a pre-monolayer oxidation step that forms an incipient hydrous oxide layer of OHads, which mediates the electrooxidation of glucose and many other organic molecules and inhibits many kinetically slow reduction process. The 'active' atoms on the electrode surface are considered to have a low lattice coordination value, and lack normal lattice stabilization energy. Polycrystalline surfaces at discontinuous areas such as grain boundaries and edges, are more easily exposed to the solution

than the bulk crystal surface, thus they are more liable to undergo pre-monolayer oxidation at lower potentials. According to the IHOAM model, electrocatalytic oxidation of glucose is initiated by the formation of hydrous species on the electrode surface followed by the chemisorption of glucose molecules. After that, the hydrous pre-monolayer could mediate the electrooxidation of absorbed glucose at significantly low potential, with the regeneration of metal surface. The surface of the 'active' metal is then oxidized again by oxygen species at certain potential and glucose is continuously oxidized during the repetitive cycling process. Both the activated chemisorption model and IHOAM model will be discussed in the following sections regarding to different electrode materials. IHOAM model explains the enhancement of electrocatalytic performance of most noble metal-based materials. The hydroxyl group also plays important role in the electrocatalytic process of nickel- and copper-based electrodes. However, in these cases the incipient hydrous pre-monolayer is formed not to induce catalysis, but rather to change the oxidation state of the metal hydroxide.

2 Nanomaterials used for electrocatalytic glucose sensing

2.1 Transition metals

Transition metals are well known to be good electrocatalysts due to either their ability to adopt multiple oxidation states and absorb other species on their surfaces to form intermediates and activate them in the reaction process. The advantages of nanostructured metallic materials are their unique physical, chemical, optical and electrical properties such as high surface-to-volume ratio, high index facets, large specific surface area, good electrical conductivity, tunable optical property and high electrocatalytic activity.^{22–28} Therefore, transition metal nanomaterials could serve as effective catalysts due to their high ratio of surface atoms with free valences to the cluster of total atoms and the resulting enhanced mass transport property. A wide range of transition metal nanomaterials have been studied in recent years for the electrocatalytic biosensing. According to the literatures, gold (Au), platinum (Pt), palladium (Pd), copper (Cu) and nickel (Ni) are the most intensively studied transition metal nanomaterials for non-enzymatic catalysis of glucose oxidation.

2.1.1 Gold. Gold nanomaterials have demonstrated excellent performance for the electrochemical non-enzymatic biosensing of glucose.^{29–46} Kurniawan *et al.*³⁹ reported a non-enzymatic glucose biosensor by layer-by-layer deposition of gold nanoparticles (Au NPs) on a thin gold electrode. The biosensor achieved a detection limit of 0.5 mM, sensitivity of $160 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and linear range up to 8 mM in 0.1 M NaOH solution. Jena and co-workers⁴⁰ fabricated an enzyme-free amperometric glucose biosensor by self-assembling gold nanoparticles on three-dimensional (3D) silicate network obtained using sol-gel method. The amperometric detection of glucose was achieved at a low potential of 0.16 V in phosphate buffer solution (PBS, pH 9.2) by the biosensor, and

the Au NPs modified electrode exhibited a detection limit of 50 nM, with sensitivity of $179 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and linear range up to 8 mM. Ma and colleagues⁴¹ reported a non-enzymatic glucose sensor by direct electrodeposition of Au NPs on the surface of indium tin oxide (ITO). The Au NPs-modified ITO electrode showed high electrocatalytic activity toward glucose in 0.01 M NaOH and 0.05 M PBS (pH 7.4). At the applied potential of 0.2 V, the biosensor showed a linear range of 0.004–5 mM in 0.01 M NaOH solution and 0.05–5 mM in 0.05 M PBS solution. The sensitivity of the electrode is $183.5 \mu\text{A mM}^{-1}$ and limit of detection (LOD) is 0.005 mM in 0.01 M NaOH solution. Zhao *et al.*⁴² developed a gold nanostructured film by a green chemistry method and employed it for non-enzymatic measurement of glucose concentration. The Au nanofilm based biosensor permits the detection of glucose in pH 7.4 PBS solution, giving a linear range up to 57.5 and 30 mM with detection limit as low as 0.72 and 3.6 μM at fixed potentials of 0.3 and -0.15 V respectively. Cherevko and Chung³² described a gold nanowire array electrode which enables both voltammetric and amperometric sensing of glucose. The voltammetric sensing achieved a linear range up to 20 mM with a sensitivity of $41.9 \mu\text{A mM}^{-1} \text{cm}^{-2}$, and a detection limit down to 30 μM ; while the amperometric detection method gave a calibration range up to 10 mM, with a remarkably high sensitivity of $309 \mu\text{A mM}^{-1} \text{cm}^{-2}$ at -0.4 V in 0.1 M NaOH solution. Recently, Xiao *et al.*⁴⁷ have reported a flexible electrode based self-assembly of Au NPs on freestanding graphene paper, which showed excellent electrocatalytic activities. The composite nanostructured electrode was employed as a non-enzymatic biosensor for the detection of both glucose and H_2O_2 in pH 7.4 PBS solution. The Au NPs-based flexible amperometric glucose biosensor showed a good linear range of 0.01–46 mM, with a sensitivity of $52.36 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and detection limit of 5 μM at applied potential of 0.08 V. What is worth mentioning is that the biosensor showed an excellent selectivity, because the detection potential is very close to 0 V, at which most of electroactive interferences in the blood did not show noticeable responsive currents. The detailed comparison of various Au nanostructured non-enzymatic electrodes is shown in Table 1.

2.1.2 Platinum. It is well known that platinum has good catalytic activity toward many compounds, especially glucose and H_2O_2 . However, the flat platinum electrode has several fatal drawbacks that prevent it from direct application in non-enzymatic biosensors. First, the surface of Pt could be seriously poisoned by many species in the physiological conditions, especially chloride anions, which strongly absorb to the surface of Pt, so that they make the electrode surface inaccessible to the analytes.⁴⁸ Second, the chemisorption of many organic species in the blood such as amino acids, ascorbic acid (AA), uric acid (UA), creatinine and epinephrine severely reduces the electrocatalytic activity of Pt electrode during the practical usage.^{49,50} Third, the selectivity of Pt electrode is poor when it is used as a biosensor because the small current responses of target molecules resulting from sluggish reaction and slow electron transfer kinetics cannot compete to the interferential current from the electroactive species.⁵¹ Last but not the least, the surface area of bulk Pt electrode is restricted by the flat geometry of Pt disk, which

Table 1 The glucose biosensing performance of various Au nanomaterials modified electrodes^a

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Au nanowire array/glass	309	Up to 10	50	-0.4 vs. Hg/HgO	0.1 M NaOH	32
Porous Au/Au E	11.8	2–10	5	+0.35 vs. SCE	PBS (pH 7.4)	44
Au NPs/Au E	179	0–8	0.05	+0.16 vs. Ag/AgCl	PBS (pH 9.2)	40
Au NPs/porous silica film	76	0.2–70	100	—	0.1 M NaOH	45
Au NPs/graphene paper	52.36	0.01–46	5	+0.08 vs. Ag/AgCl	PBS (pH 7.4)	47
Layer-by-layer Au NPs/Au E	160	Up to 8	500	—	0.1 M NaOH	39
Au NPs/ITO	183.5	0.004–0.5	—	+0.2 vs. SCE	0.01 M NaOH	41
Au nanofilm	57.5	Up to 57.5	0.72	+0.3 vs. SCE	PBS (pH 7.4)	42
Au micropillar arrays	13.2	0.5–9	60	—	PBS (pH 7.4)	37
Au nanotube arrays	1.13	1–42.5	10	+0.25 vs. SCE	PBS (pH 7.4)	31
Au nanocorals	22.6	0.05–30	10	+0.2 vs. Ag/AgCl	PBS (pH 7.4)	46
Au NPs/chitosan/GCE	—	0.4–10.7	370	—	PBS (pH 7.1)	29

^a Au NPs: Au nanoparticles; Au E: Au electrode; ITO: Indium tin oxide; GCE: glassy carbon electrode.

results in poor sensitivity of the biosensor.⁵² The aforementioned problems associated with bulk platinum electrode for non-enzymatic glucose sensing could be alleviated by using nanostructured platinum materials.

Nanoporous platinum is the most intensively studied Pt nanomaterials for non-enzymatic glucose detection because they show remarkably high sensitivity and excellent property to resist interferences due to the increased roughness factor on the electrode surface. The use of nanoporous Pt electrode for non-enzymatic glucose sensing was first investigated by Park *et al.*⁵³ The roughness of nanoscopic dimension of Pt could selectively enhance the current of sluggish reaction, thus the porous Pt electrode showed much more sensitive current signals of glucose than to other electroactive compounds, such as AA and acetamidophenol. In addition, the biosensor showed excellent antifouling property. A good sensitivity of $9.6 \mu\text{A mM}^{-1} \text{cm}^{-2}$ with linear range up to 10 mM was observed reproducibly in the presence of high concentration of chloride ions. Following this study, a variety of nanoporous Pt electrodes^{54–59} have been fabricated for the non-enzymatic detection of glucose with enhanced sensitivity. Except nanoporous Pt electrode, Pt nanoparticles^{60–62} and other forms of Pt nanomaterials^{63–66} have also been studied. For example, highly ordered Pt nanotubule arrays were fabricated by electrodeposition and used for enzymeless glucose sensing in either 0.5 M H_2SO_4 solution or in PBS (pH 7.4).⁶⁴ The biosensor exhibited a linear range of 2–14 mM, with a

sensitivity of $0.1 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and detection limit of 0.1 μM glucose in PBS. Electrode modified with 3D dendritic Pt nanostructures⁶⁵ was employed for electrocatalytic glucose biosensing without enzyme in PBS solution (pH 7.4). It achieved a linear range of 1–20 mM, with a detection limit down to 1.2 μM and a sensitivity of $12.1 \mu\text{A mM}^{-1} \text{cm}^{-2}$. The glucose biosensing performance of various nanostructured Pt electrodes is compared in Table 2.

2.1.3 Palladium. There has been an increasing interest in using palladium (Pd) and its hybrid with carbon nanomaterials as electrocatalyst for non-enzymatic biosensing in recent years due to its high electrocatalytic activity and low cost.^{67–72} In the application of glucose sensor, Bai *et al.*⁶⁹ synthesized a porous tubular Pd nanostructure with CdS modified alumina as template. The porous tubular Pd-modified screen printed electrode (SPE) achieved a large linear range of 0.1–58 mM and low detection limit of 0.08 mM (S/N = 3). The amperometric sensing of glucose was conducted by the modified electrode in PBS solution (pH 8.1) at 0.6 V (vs. Ag/AgCl). Meng and his colleagues⁷⁰ developed a hybrid nanomaterial of Pd nanoparticle/single-walled carbon nanotubes (SWCNTs), which showed high sensitivity toward non-enzymatic glucose oxidation in PBS solution (pH 7.4). The Pd/SWCNTs-modified GCE exhibited excellent anti-poisoning property in the presence of high concentration of chloride ions. In the respect of amperometric sensing performance, the hybrid material modified electrode achieved a fast response of 3 s, low

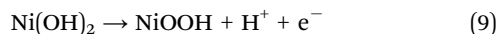
Table 2 Comparison of the glucose biosensing performances of various nanostructured Pt electrodes

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Pt mesoporous film	9.6	0–10	—	+0.4 vs. Ag/AgCl	PBS (pH 7.4)	53
3D ordered macroporous Pt	31.3	1–10	0.1	+0.5 vs. SCE	PBS (pH 9.18)	55
Nanoporous Pt	291	0–10	—	+0.4 vs. Ag/AgCl	PBS (pH 7.4)	56
3D nanoporous Pt	642	0.1–1.5	—	+0.4 vs. Ag/AgCl	PBS (pH 7.4)	54
Nanoporous Pt microsensor	37.5	0.05–30	—	+0.4 vs. Ag/AgCl	PBS (pH 7.4)	58
Nanoporous Pt thin film	1.65	1–10	97	+0.4 vs. Ag/AgCl	PBS (pH 7.4)	59
Ultrafine Pt NPs	137.7	0.2–3.2	5	+0.6 vs. Ag/AgCl	PBS (pH 6.8)	61
Pt/MWCNTs ^a	11.83	1–23	50	+0.5 vs. Ag/AgCl	0.1 M NaOH	62
Pt nanotube arrays	0.1	2–14	1.0	+0.4 vs. SCE	PBS (pH 7.4)	64
3D dendritic Pt nanostructures	12.1	1–20	1.2	+0.5 vs. SCE	PBS (pH 7.4)	65

^a MWCNTs: multi-walled carbon nanotubes

detection limit of $0.2 \pm 0.05 \mu\text{M}$, good linear range of 0.5–17 mM and high sensitivity of $160 \mu\text{A mM}^{-1} \text{cm}^{-2}$ at a low operating potential of -0.35 V vs. SCE . Similarly, Chen *et al.*⁷¹ also reported a hybrid material of functional CNTs (FCNTs) supported Pd nanoparticles (Pd NPs) for the non-enzymatic sensing of glucose. The modified electrode also exhibited excellent anti-poisoning and anti-interference properties. Amperometric sensing of glucose by the Pd NPs/FCNTs-modified electrode was performed at $+0.4 \text{ V vs. SCE}$ in 0.1 M NaOH solution. The biosensor showed a large linear range of 0–46 mM with a sensitivity of $11.4 \mu\text{A mM}^{-1} \text{cm}^{-2}$. Wang and his colleagues⁶⁸ have recently reported a hybrid material of well-dispersed Pd NPs on graphene oxide for the non-enzymatic glucose sensor. In 0.1 M NaOH solution at the operation potential of 0.4 V vs. SCE , the biosensor achieved a linear range of 0.2–10 mM with fast response of 2 s. In another work, Lu *et al.*⁷² fabricated a non-enzymatic glucose biosensor based on *in situ* synthesized Pd NPs/Nafion-functionalized graphene nanohybrid. The biosensor could be applied for the quantification of glucose in the concentration range of 10 μM to 5 mM with a low detection limit of 1 μM in 0.1 M NaOH solution at $+0.4 \text{ V vs. SCE}$.

2.1.4 Nickel. Non-enzymatic glucose oxidation based on Nickel electrode has been intensively studied. However, the reaction mechanism is different from that of Au, Pt and Pd-based electrodes. It has been reported by Fleischmann⁷³ that the catalytic component is Ni(III) oxyhydroxide and oxidation of glucose is mainly based on the Ni(OH)₂/NiOOH redox couple. The surface bond change reaction can be explained by the following equation:



Immersion of Ni electrode into alkaline solution results in the formation of Ni(OH)₂, and upon electrooxidation the corresponding NiOOH species are formed. Similar to Au, Pt and Pd electrodes, the rate determining step of glucose oxidation at Ni-based electrodes is the process of abstraction of hydrogen atom at C1 carbon. Upon the formation of Ni(III) oxyhydroxide, glucose will be oxidized immediately and produce a radical intermediate, which in turn reacts rapidly with hydroxyl anions in the solution to form gluconolactone.

Ni nanomaterials based non-enzymatic glucose sensors has been reported in recent years with enhanced performance compared to bulk Ni electrode.^{74–81} Wang's group⁷⁸ has reported highly ordered Ni nanowire arrays (Ni NWA) for the non-enzymatic quantification of glucose. The Ni NWA-based electrode showed a wide linear range from 0.5 μM to 7.0 mM, with a high sensitivity of $1043 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and a low detection limit of 0.1 μM . Liu *et al.*⁷⁷ reported a non-enzymatic glucose biosensor based on electrospun Ni nanoparticle-loaded carbon fibre paste electrode. The biosensor exhibited a low detection limit of 1 mM with a linear range of 2 mM to 2.5 mM. Ni nanoparticles (Ni NPs) decorated straight multi-walled carbon nanotubes (SMWNTs) has also been fabricated and used for enzymeless glucose detection.⁷⁹ The Ni NPs/SMWNTs hybrid material based biosensor achieved a linear range from 1 μM to 1 mM with a detection limit of 500 nM (3σ). In addition, the nanohybrid modified electrode exhibited

excellent anti-interference property and robust stability. Ni-based nanomaterials seem to be the most sensitive electrode materials for non-enzymatic glucose oxidation, with reported sensitivity as high as $\text{mA mM}^{-1} \text{cm}^{-2}$ in many publications.^{78,80,81} The highest sensitivity reported is Ni nanoflakes on Ti substrate,⁸⁰ which achieved a current density of $7.32 \text{ mA mM}^{-1} \text{cm}^{-2}$. However, the most serious problem of Ni nanomaterials based non-enzymatic glucose sensors is their inability to practically detect glucose in physiological pH solution, because electrocatalytic performance of NiOOH is highly dependent on the presence of hydroxyl ions in the electrolyte medium.⁸² In addition, although Ni-based electrode does not have the problem of surface-fouling by chloride ions,⁷⁷ it suffers from poor selectivity. According to Fleischmann's study,⁷³ Ni-based electrode is also capable to oxidize a number of other small organic molecules at the same potential immediately after the formation of NiOOH. Most small organic molecules could oxidize on Ni electrode surface at $\sim +0.5 \text{ V}$ in alkaline solution. Except for glucose, ethanol is the major component that could easily oxidize on Ni-based electrodes.

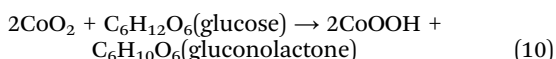
2.1.5 Copper. Cu-based electrodes work in a similar way as Ni-based electrodes toward the electrooxidation of glucose. The catalytic reaction relies on the redox couple of Cu(III)/Cu(II), but the electron transfer process between Cu(II)/(III) is not as obvious as for Ni-based electrodes. Nanostructured Cu based non-enzymatic glucose sensors have been increasingly reported in recent years.^{83–95} Huang *et al.*⁹³ investigated the electron transfer mechanisms of Cu foil, Cu nanoparticles (Cu NPs) and Cu nanobelts (Cu NBS) and compared the non-enzymatic glucose sensing performance between Cu NPs and Cu NBS modified electrodes. Cu NBS showed significantly higher reduction/oxidation responses than Cu foil and Cu NP electrodes in PBS buffer and the amperometric response of Cu NB electrode is significantly larger than Cu NP toward glucose oxidation in 50 mM NaOH electrolyte. The Cu NBS-based glucose sensor exhibited a high sensitivity of $79.8 \mu\text{A mM}^{-1} \text{cm}^{-2}$ with a detection limit of 10 μM . The oxidation current was linearly dependent to the glucose concentration in the range of 10 μM to 1.13 mM. The studies of Cu NPs/MWCNTs and Cu NPs/SWCNTs toward non-enzymatic glucose oxidation were conducted by Kang⁹⁴ and Male,⁹⁵ respectively. The Cu NPs/MWCNTs modified GCE showed a linear range for the glucose detection of 0.7 μM to 3.5 mM with a high sensitivity of $17.76 \mu\text{A mM}^{-1} \text{cm}^{-2}$, a low LOD of 0.21 μM , and a fast response time of within 5 s. The response time and LOD of Cu NPs/SWCNTs-modified GCE are 10 s and 250 nM, respectively. A linear relationship between current response and glucose concentration was observed up to 500 μM , with a sensitivity of $256 \pm 3 \mu\text{A mM}^{-1} \text{cm}^{-2}$. A further comparison of Ni and Cu nanomaterials based non-enzymatic glucose biosensors is shown in Table 3. We can see from the table that the glucose detection with Ni and Cu nanomaterials modified electrode was usually conducted in alkaline solution. Although these electrodes could easily achieve a sensitivity as high as several $\text{mA mM}^{-1} \text{cm}^{-2}$, the linear range was seriously diminished and amperometric sensing usually required a very high potential ($>0.6 \text{ V}$), at which the interferential responses were difficult to be avoided.

Table 3 Non-enzymatic glucose biosensing performance of nanostructured Ni and Cu based electrodes

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Ni nanowire arrays	1043	0.0005–7	0.1	+0.55 vs. SCE	0.1 M NaOH	78
Ni NP/carbon fiber paste	420.4	0.002–2.5	1	+0.6 vs. Ag/AgCl	0.1 M NaOH	77
Ni NP/SMWNTs	1438	0.001–1	0.5	+0.4 vs. SCE	0.1 M NaOH	78
Ni nanoflakes	7320	0.05–0.6	1.2	+0.5 vs. SCE	0.5 M NaOH	80
Cu NPs	3600	0.003–10	0.7	+0.7 vs. SCE	0.1 M NaOH	83
Cu polyhedron nanostructures	—	0.2–4.2/4.2–32.1	70	+0.5 vs. SCE	0.1 M NaOH	88
Cu nanowires	927	0.002–0.075	1	+0.7 vs. SCE	0.1 M NaOH	91
Cu nanostructures	420	Up to 3	0.035	+0.6 vs. Ag/AgCl	0.05 M NaOH	92
Cu nanobelts	4433	0.01–1.13	10	+0.6 vs. Ag/AgCl	0.05 M NaOH	93
Cu nanocluster/MWCNTs	253	0.7–3.5	0.21	+0.65 vs. Ag/AgCl	0.02 M NaOH	94
Cu nanocubes /MWCNTs	1096	Up to 7.5	1	+0.55 vs. Ag/AgCl	0.1 M NaOH	89
Cu NPs/MWCNTs	714	0.01–0.3	0.5	+0.35 vs. SCE	0.02 M NaOH	87
Cu NPs/SWCNTs	3657	Up to 0.5	0.25	+0.65 vs. Ag/AgCl	0.02 M NaOH	95
Cu NPs/graphene	—	Up to 4.5	0.5	+0.5 vs. SCE	0.1 M NaOH	84
Cu NPs/graphene	607	0.005–1.4	0.2	+0.5 vs. SCE	0.1 M NaOH	85

2.2 Metal oxides and complexes

2.2.1 Cobalt oxide. Cobaltous oxide (CoO), cobaltic oxide (Co_2O_3) and cobaltous oxide (Co_3O_4) are three well known polymorphs of cobalt oxide. Cobalt oxide had not been explored for non-enzymatic electrochemical biosensing until the first study by Ding *et al.*,⁹⁶ who investigated the mechanism of electrospun Co_3O_4 nanofibers (Co_3O_4 NFs) toward electrocatalytic oxidation of glucose and employed Co_3O_4 NFs/Nafion modified GCE for sensitive and selective glucose detection. Ding proposed that the electrocatalytic property of Co_3O_4 NFs in alkaline solution was due to the conversion of Co_3O_4 to CoO_2 , which could in turn catalyze the oxidation of glucose according to the following equation:

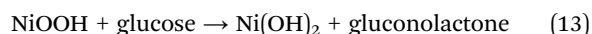
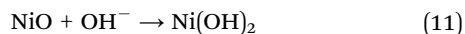


The Co_3O_4 NFs-based glucose sensor showed a fast response within 7 s, a high sensitivity of $36.25 \mu\text{A mM}^{-1} \text{cm}^{-2}$, a detection limit of $0.97 \mu\text{M}$ with a linear range up to 2.04 mM. Followed by this Co_3O_4 study, Kung *et al.*⁹⁷ reported acicular cobalt oxide nanorods (CoO NRs) synthesized by chemical bath deposition for the non-enzymatic detection of glucose. The study claimed that CoO NRs-modified electrode could selectively detect glucose without the casting of Nafion, which is a negatively charged membrane capable to exclude negatively charged interferential molecules. The sensitivity and LOD of CoO NRs-based glucose sensor are $571.8 \mu\text{A mM}^{-1} \text{cm}^{-2}$ and $0.058 \mu\text{M}$, which is 15 times higher and 10 times lower than Ding's electrode. In addition, the biosensor also exhibited a wider linear range up to 3.5 mM and lower detection potential of 0.5 V than Ding's sensor. Simultaneously, Dong *et al.*⁹⁸ reported a composite material of 3D graphene- Co_3O_4 nanowires as a freestanding electrode for non-enzymatic glucose sensing. The biosensor achieved a sensitivity of $3.39 \text{mA mM}^{-1} \text{cm}^{-2}$ and a LOD of 25 nM, which are nearly 6 times higher and 2 times lower than those of CoO NRs-modified electrode in Kung's study. However, the up to 80 μM linear range of 3D graphene/ Co_3O_4 nanowire electrode is much smaller than those of both Ding's and Kung's biosensors. Very recently, a graphene/cobalt oxide-based

needle electrode has been reported by the same group of Dong.⁹⁹ The biosensor showed a capability for glucose detection in micro-droplets within the linear concentration range of 50–300 μM .

2.2.2 Copper oxide. Copper oxide seems to be the most extensively studied metal oxide for non-enzymatic glucose biosensing in recent years.^{100–113} The mechanism of glucose electrochemical oxidation on copper oxide electrode is similar to Cu electrode. Zhuang *et al.*¹¹⁴ fabricated a non-enzymatic glucose sensor based on CuO nanowires modified Cu electrode, which exhibited substantially lower overpotential than bare Cu electrode toward glucose oxidation. At an applied potential of 0.33 V (vs. Ag/AgCl), the biosensor showed a sensitivity of $490 \mu\text{A mM}^{-1} \text{cm}^{-2}$, with a linear response over the concentration range from 0.4 μM to 2 mM and a LOD of 49 nM ($\sigma = 3$). Similarly, Zhang *et al.*¹¹² reported CuO nanowires and Wang *et al.*¹⁰⁹ reported the CuO/Cu nanowire composite modified GCE for enzymeless glucose sensing. The former electrode achieved a fast response (<2 s) with a low detection limit of 45 nM, while the latter biosensor exhibited a wide linear range from 0.1 to 12 mM for glucose detection. An enzymeless biosensor based on flower-like Cu_xO modified Cu electrode was investigated by Li.¹⁰⁴ The sensor achieved a high sensitivity of $1.62 \text{mA mM}^{-1} \text{cm}^{-2}$ over the linear concentration range up to 4 mM. Except for the nanowire structure, CuO nanofibers¹¹⁵ and CuO nanospheres¹¹⁶ have also been investigated for the glucose electrocatalysis. However, it seems that the biosensing performance of CuO nanowires-modified electrodes outperform others. Additionally, Cu_2O NPs were decorated on MWCNTs to improve the sensitivity of the copper oxide based biosensors.¹¹³ In a study by Jiang,¹¹⁷ CuO NPs modified MWCNTs array electrode exhibited an extremely high sensitivity of $2.596 \mu\text{A mM}^{-1} \text{cm}^{-2}$ over the concentration range up to 1.2 mM with a LOD of 0.2 μM . The CuO NPs/MWCNTs electrode also achieved a very fast response within 1 s upon the addition of 0.1 mM glucose.

2.2.3 Nickel oxide. The electrochemical glucose oxidation on NiO-modified electrode is based on the redox couple of $\text{Ni}(\text{OH})_2/\text{NiOOH}$ derived from NiO,¹¹⁸ similar to that of Ni-based electrode. The reaction mechanism is indicated by the following equations:



A variety of NiO nanomaterials have reported in recent years by a number of groups for the study of non-enzymatic glucose sensing performance.^{119–126} Mu and colleagues¹¹⁸ have investigated the electrochemical properties and electroanalytical performance of nano-NiO modified CPE toward the oxidation of glucose. The biosensor showed a quick response to the glucose within 5 s and a calibration plot in the concentration range of 1–110 μM , with a sensitivity of $43.9 \text{ nA } \mu\text{M}^{-1} \text{ cm}^{-2}$ and a LOD of $0.16 \mu\text{M}$. NiO/MWCNTs nanocomposite-based enzymeless glucose biosensors have been reported by Shamsipur¹²⁴ and Zhang,¹²⁵ respectively. MWCNTs were found to improve the reactivity of NiO for glucose oxidation remarkably. Shamsipur's electrode showed a wide linear range of $0.2 \text{ mM}–20 \text{ mM}$ with a LOD of 0.16 mM , while Zhang's biosensor exhibited a high sensitivity of $1.77 \text{ mA mM}^{-1} \text{ cm}^{-2}$ with linear range up to 7 mM and a LOD of $2 \mu\text{M}$.

2.2.4 Other metal oxides. A few other nanostructured metal oxides such as MnO_2 ,¹²⁷ M_3O_4 ,¹²⁸ ZnO ,^{129,130} RuO_2 ,^{134,135} Ag_2O ,¹³¹ Fe_2O_3 ¹³² and FeOOH ¹³³ have also been reported for the non-enzymatic biosensing. For example, Chen *et al.*¹²⁷ reported an amperometric non-enzymatic glucose sensor based on $\text{MnO}_2/\text{MWCNTs}$. Recently, a nanocomposite of hierarchically structured $\text{Mn}_3\text{O}_4/3\text{D}$ graphene was reported by Si *et al.* for catalytic oxidation of glucose and biosensing.¹²⁸ ZnO nanorods and ZnO nanoparticles modified MWCNTs have been reported by Dar *et al.*¹²⁹ and Baby *et al.*¹³⁰ respectively for the fabrication of non-enzymatic glucose biosensors. RuO_2 have been investigated by a few groups for the non-enzymatic detection of glucose^{134,135} and phenolic compounds.^{136,137} The non-enzymatic glucose sensors have also been reported by using Fe_2O_3 nanowire arrays modified electrode by Cao *et al.*¹³² Recently Fang *et al.*¹³¹ reported Ag_2O nanowalls grown on Cu substrate as a non-enzymatic glucose biosensor. The Ag_2O nanowalls showed higher electrocatalytic activity than Ag_2O nanoflowers and Ag_2O nanospindles toward glucose oxidation in alkaline solution. The biosensing performance of these metal oxide nanomaterials modified electrodes are summarized in Table 4.

2.2.5 Metal complexes. Some metal complexes, such as metallophthalocyanines^{138–145} and metal hexacyanoferrate^{146–151} were reported to exhibit excellent electrocatalytic activities toward the oxidation of small molecules. Although metal complexes were usually used in collaboration with GOx for glucose sensing,^{141–150} there are several publications that reported the direct electrocatalytic oxidation of glucose by metal complexes in alkaline solution.^{138–140,151} In a study by Barrera *et al.*,¹³⁸ the reactivity of cobalt phthalocyanine (CoPc) and its various substitutes such as cobalt hexadecafluorophthalocyanine (CoF_{16}Pc), cobalt octaethylhexyloxyphthalocyanine (CoOEHPc), cobalt tetraaminophthalocyanine (CoTAPc) and cobalt tetrasulfophthalocyanine (CoTSPc) toward electrooxidation of glucose were investigated. The study concluded that the unsubstituted CoPc had the best electrocatalytic activity for glucose oxidation. Nevertheless, Ozcan *et al.*¹³⁹ reported a non-enzymatic glucose biosensor based on CoTSPc modified over-oxidized polypyrrole nanofiber. The study claimed that CoTSPc exhibited excellent activity for electrocatalysis of glucose in alkaline solution. The resulting biosensor based on CoTSPc achieved a large linear range of $0.25–20 \text{ mM}$, with a LOD of 0.1 mM at 3σ , a highly reproducible response with R.S.D of 2.7%, good resistance to interferences and long-term stability. The non-enzymatic glucose sensor based on metal hexacyanoferrate was reported by Wang,¹⁵¹ who successfully employed nickel hexacyanoferrate nanoparticle film modified GCE for the amperometric quantification of glucose concentration in alkaline solution. The biosensor achieved a linear range of $5 \mu\text{M}–2.5 \text{ mM}$, with a low LOD of $1.25 \mu\text{M}$ at 3σ . The glucose oxidation mechanism of nickel hexacyanoferrate electrode, as proposed by the study, is similar to that of Ni and NiO based electrodes, relying on the formation of NiOOH and reduction of NiOOH to Ni(OH)_2 , as shown by eqn (12) and (13).

2.3 Bimetallic systems

The bimetallic material could become a superior catalyst that exhibits desired electronic property and very high catalytic activity. Alloys, adatoms and metal (oxide)/metal oxide composites are the major forms of bimetallic electrocatalysts. Due to the synergistic effect of the two materials, the bimetallic systems can significantly enhance the electrooxidation of glucose and reduce the interference and poisoning effect of the electrode. In addition, most of the bimetallic systems were able to catalyse the glucose oxidation in

Table 4 Electroanalytical glucose biosensing performance of some nanostructured metal oxides modified electrodes

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{ cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Co_3O_4 nanofibers	36.25	Up to 2.04	0.97	+0.59 vs. Ag/AgCl	0.1 M NaOH	96
$\text{Co}_3\text{O}_4/3\text{D}$ graphene	3390	Up to 0.08	0.025	+0.58 vs. Ag/AgCl	0.1 M NaOH	98
NiO/MWCNTs	1770	Up to 7	2	+0.5 vs. Ag/AgCl	0.12 M NaOH	125
CuO nanofibers	431.3	0.006–2.5	0.8	+0.4 vs. SCE	0.1 M NaOH	115
Cu_xO nanowires	1620	Up to 4.0	49	+0.5 vs. Ag/AgCl	0.1 M NaOH	104
CuO NP/MWCNTs	2596	Up to 1.2	0.2	+0.4 vs. Ag/AgCl	0.1 M NaOH	117
$\text{MnO}_2/\text{MWCNTs}$	396	Up to 28	—	+0.3 vs. Ag/AgCl	0.1 M NaOH	127
$\text{Mn}_3\text{O}_4/3\text{D}$ graphene	360	0.1–8	10	+0.4 vs. Ag/AgCl	0.1 M NaOH	128
ZnO nanorods	5.6	0.01–10	0.5	—	PBS (pH 7.4)	129
Ag_2O nanowalls	—	0.2–3.2	10	+0.4 vs. Ag/AgCl	0.1 M NaOH	131
Fe_2O_3 nanowire arrays	726	0.015–8	6	+0.52 vs. SCE	PBS (pH 7.5)	132

physiological pH solution. Therefore, the study of bimetallic materials for non-enzymatic glucose sensing has attracted tremendous research interest in recent years.

2.3.1 Alloys. A wide variety of alloy nanomaterials, including Pt–Pb,^{152–155} Pt–Ru,^{156,157} Pt–Ir,¹⁵⁸ Pt–Ni,^{159–161} Pt–Pd,¹⁶² Au–Pt,^{163–168} Au–Ag,¹⁶⁹ Au–Ru,¹⁷⁰ Au–Cu^{171,172} and Ni–Cu^{173,174} have been reported in recent years for non-enzymatic biosensing. Among them, Pt based alloy nanomaterials are most popular since they exhibit the highest catalytic activity toward the electrooxidation of small organic compounds.¹⁷⁵ Sun *et al.*¹⁵³ compared alloys with different combinations of Pt, Pb, Au, Pd and Rh, and concluded that Pt and Pb comprise the best composition (*i.e.*, Pt₂Pb) that achieved the highest catalytic activity for glucose oxidation. In addition to its higher sensitivity, Pt₂Pb also exhibited excellent selectivity because it could catalyse the oxidation of glucose at negative potentials, where most of the interferences including AA, UA and AP are not responsive. However, the Pt₂Pb electrode did not alleviate the problem of surface poisoning by chloride ions, which remains a critical challenge for non-enzymatic glucose sensors. The performance of Pt–Pb alloy based non-enzymatic glucose sensor was improved by Wang *et al.*,¹⁵⁴ who reported that the PtPb nanoporous network modified Ti electrode was highly resistant to the poisoning of chloride ions. In addition, the biosensor also exhibited excellent anti-interference property since the nanoporous PtPb electrode was capable of amperometric sensing glucose at a remarkably low potential, *ca.* –80 mV (*vs.* Ag/AgCl) in PBS solution (pH 7.4). Similarly, Bai *et al.*¹⁵² synthesized PtPb nanowire for the non-enzymatic detection of glucose. The biosensor achieved a high sensitivity of 11.25 $\mu\text{A mM}^{-1} \text{cm}^{-2}$ with a linear range up to 11 mM and a detection limit down to 8 μM ($\sigma = 3$). The non-enzymatic glucose sensor based on hybrid material of PtPb alloy nanoparticles decorated MWCNTs has also been reported.¹⁵³ Although the nanocomposite modified electrode achieved a slightly improved sensitivity of 18 $\mu\text{A mM}^{-1} \text{cm}^{-2}$, it was compromised with a shorter linear range which is only up to 5 mM. Interestingly, Xiao *et al.*¹⁵⁷ compared the non-enzymatic glucose sensing performance of PtM (M = Ru, Pd and Au) nanoparticles on the composite film of MWCNTs/ionic liquid (IL) and found that PtRu (1 : 1)/MWCNTs/IL modified GCE exhibited the strongest electrocatalytic activity toward glucose

oxidation in neutral pH media. The biosensor achieved a linear range up to 15 mM, with a sensitivity of 10.7 $\mu\text{A mM}^{-1} \text{cm}^{-2}$ and LOD of 50 μM . The non-enzymatic glucose biosensor based on CNTs supported PtRu alloy nanoparticles has also been investigated by Li and colleagues,¹⁵⁶ who reported a similar linear range to Xiao's work, but with a higher sensitivity of 28.26 $\mu\text{A mM}^{-1} \text{cm}^{-2}$ and lower LOD of 0.25 μM . On the other hand, the catalytic performances of Cu based alloys of Ni, Fe and Mn have been investigated by Yeo.¹⁷³ It was observed that the anodic response of Mn₅Cu₉₅ to glucose in 0.1 M NaOH solution is larger than other electrodes possibly due to the pre-adsorption of glucose molecules on Mn sites. NiCu alloy based non-enzymatic glucose biosensor was also reported by Jafarian *et al.*¹⁷⁴ Unfortunately, the above mentioned Cu alloyed nanomaterials are not able to determine the glucose concentration in blood since they could not catalyse the glucose oxidation under physiological conditions. The recently reported a 3D Au@nanoporous Cu (Au@NPC) core-shell composite material may be promising to solve the biosensing problem associated with Cu alloyed nanomaterials.¹⁷² As was reported, the Au@NPC alloy showed strong oxidation peak of glucose in 0.1 M PBS (pH 7.4) and the nanocomposite modified GCE achieved a linear response for glucose oxidation in the range of 3–8 mM in PBS. Nevertheless, other reported Au–Cu nanoparticle alloy modified carbon electrode did not show the feature of glucose sensing in neutral pH solution.¹⁷¹ A more detailed comparison of the analytical performance of alloy nanomaterials based non-enzymatic glucose biosensors is listed in Table 5.

2.3.2 Adatoms. Adatoms are a sub-monolayer of metals such as Pb, Bi, Hg and Tl that formed on the surface of Au and Pt electrode by under-potential-deposition in acidic solution. The adatoms could enhance the anodic current response of glucose in alkaline solution by 1–2 orders of magnitude^{176,177} and inhibit the poisoning side reactions on Pt electrode by repelling the hydrogen adsorption.¹⁷⁸

Pletcher²⁰ observed that partial coverage of Au and Pt electrodes with metal adatoms such as Pb could remarkably improve long-term catalytic activity of the electrode and reduce the formation of poisonous species on the electrode surface. It was proposed that Pb atom could interact with two Pt sites to form a surface of Pt atom pairs, which limited the active sites

Table 5 Non-enzymatic glucose sensing performance of various alloy nanomaterials modified electrodes

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Pt ₂ Pb NPs	—	0–10	—	–0.15 <i>vs.</i> SCE	PBS (pH 7.4)	153
PtPb nanoporous networks	10.8	1–16.9	—	–0.08 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	154
PtPb nanowire arrays	11.25	Up to 11	8	–0.2 <i>vs.</i> SCE	PBS (pH 7.4)	152
PtPb NPs/MWCNTs	18	Up to 5	7	–0.15 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	155
PtRu/MWCNTs/IL	10.7	0.2–15	50	–0.1 <i>vs.</i> SCE	PBS (pH 7.4)	157
PtRu NPs/MWCNTs	28.26	1–15	0.25	+0.55 <i>vs.</i> Ag/AgCl	0.1 M NaOH	156
PtNi nanowires	920	0.002–2	1.5	+0.45 <i>vs.</i> SCE	0.1 M NaOH	160
PtNi/g–raphene	20.42	Up to 35	10	–0.35 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	159
PtIr NPs	93.7	—	—	+0.1 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	158
PtAu/MWCNTs	10.71	Up to 24.44	10	+0.3 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	167
PtAu/C nanocomposites	4.7	0–10	2	+0.35 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	168
AuRu NPs	38.3	0–15	269	–0.65 <i>vs.</i> Ag/AgCl	0.1 M NaOH	170
Au@nanoporous Cu	—	3–8	—	+0.27 <i>vs.</i> Ag/AgCl	PBS (pH 7.4)	172

from poisoning across the electrode surface. Au electrodes with adatoms of Ag^{179,180} and Hg¹⁸¹ have also been explored. Aoun *et al.*^{179,180} investigated the electrocatalytic oxidation of glucose on single-crystalline gold electrode with a variety of adatoms including Cu, Ag, Ru, Pt, Pd, and Cd. The highest catalytic activity and largest negative shift of the overpotential for glucose oxidation was achieved by the Au electrode with 1/3 monolayer of Ag adatoms. Glucose was readily oxidized on the electrode at -0.5 V (*vs.* Ag/AgCl), where most of the interferential species are not reactive. In another study, Hg adatoms on Au also allows for vast enhancement of the glucose oxidation current compared to bare Au electrode in alkaline solution.¹⁸¹ It was supposed that the Hg adatoms increased the amount of absorbed OH⁻ on Au electrode that results in the improvement of the oxidation current response.

2.3.3 Composites. Recent years has seen the increasing research interest in using metal (oxide)/metal oxide nanocomposites for non-enzymatic glucose sensing. As reported, a number of materials, such as Ag/NiO,¹⁸² Pt/NiO,⁶⁶ Cu/NiO,⁹⁰ Cu/ZnO,¹⁸³ Cu/CuO,^{108,111,184} Pd/CuO,¹⁸⁵ TiO₂/CuO¹⁰⁵ and CdO/NiO¹²³ exhibited enhanced glucose sensing performance compared to the metal and metal oxide used alone. For example, the Ag/NiO nanofiber exhibited a larger linear range, lower LOD and higher sensitivity than porous Ag and NiO nanofiber at the applied potentials of 0.1 V and 0.6 V, respectively.¹⁸² The Pt/NiO nanofibers showed a vastly improved sensitivity and detection limit compared to NiO nanofiber and Pt nanofiber alone at the potential of 0.6 V.⁶⁶ The sensitivity of NiO–CdO nanofiber for non-enzymatic glucose detection at 0.6 V was 6.5 fold higher than that of pure NiO, in the meantime the linear range was wider and the LOD was lower.¹²³ The biosensing performance of these metal (oxide)/metal oxide composite materials are compared in Table 6.

2.4 Carbon

Carbon based materials are the most widely used substrates for the fabrication of electrochemical biosensors due to their electronic conductivity and electrochemical inertia. The screen printed enzymatic electrodes have been industrialized for revolutionising personal glucose monitors since 1990.^{186,187} Glassy carbon electrode (GCE), carbon paste electrode (CPE) and boron doped diamond (BDD) are the most widely used electrodes in laboratories for electrochemical study and biosensor research. Due to its electrochemical inactivity, bare GCE could only exhibit very small anodic current response to

the addition of glucose, according to the investigation by Vassilyev *et al.* in 1985.^{51,175} CPE has been widely employed for research purposes because of its simple preparation, low cost and easily renewable surface. BDD electrodes have found increasing applications for electrocatalysis in the past 25 years. With very low capacitive current, highly inert surface, resistance to fouling and wide potential window,^{81,188} BDD is an ideal electrode substrate for surface modification and electrochemical biosensing.

Various new carbon materials have emerged in the last decade with the rapid development of nanotechnology. Among them, nanostructured carbon materials such as fullerene, CNTs, carbon nanofibers, graphene and doped diamond-like materials have been intensively studied as enzymatic and non-enzymatic electrochemical biosensors.¹⁸⁹ Due to their good conductivity, high surface area, ease of functionalization and good biocompatibility, the nanostructured carbon materials showed great promise to improve the performance of electrochemical glucose biosensors. In most reported biosensors they still serve as inert supporting materials for catalytic components such as enzymes and electrocatalysts, but recently a number of studies claimed that some carbon nanomaterials, such as CNTs, exhibit direct electrochemical activities. In the following subsections we explore the recent advances of non-enzymatic electrochemical glucose biosensors based on nanostructured BDD, CNTs, graphene and a number of other carbon nanomaterials.

2.4.1 Boron doped diamond. Although it was reported that the bare BDD electrodes had a lack of electrochemical activity and were not responsive to glucose in most literatures,^{75,81,189–191} some studies reported direct glucose oxidation on unmodified BDD electrodes.^{192–194} The first observation was done in 2005 by Lee *et al.*¹⁹² who annealed the commercial polycrystalline BDD electrode by hydrogen flame before electrochemical study. The glucose oxidation peak appeared in alkaline solution at 0.65 V (*vs.* Ag/AgCl), which is similar to the oxidation behaviour of polyamines.¹⁹⁵ The reaction mechanism could be represented by the following equation:



Where OH* is the absorbed hydroxyl radicals, R is the absorbed organic species (polyamines, glucose, etc), M and M' are the different adsorption sites across the BDD electrode. The oxidation of polyamines involves the adsorption of hydroxyl radicals and polyamines on different sites of BDD

Table 6 Non-enzymatic glucose sensing performance of metal (oxide)/metal oxide modified electrodes

Electrode materials	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	Linear range (mM)	LOD (μM , S/N = 3)	Operation potential (V)	Medium	Ref.
Ag/NiO nanofibers	19.3/170.2	Up to 0.59/up to 2.63	1.37/0.72	+0.1/+0.6 <i>vs.</i> Ag/AgCl	0.1 M NaOH	182
Pt/NiO nanofibers	180.8	Up to 3.67	0.313	+0.6 <i>vs.</i> Ag/AgCl	0.1 M NaOH	66
Porous Cu/NiO nanocomposites	171.8	0.5–5	0.5	+0.4 <i>vs.</i> Ag/AgCl	0.1 M NaOH	90
Cu NPs/ZnO	—	0.001–1.5	0.2	+0.8 <i>vs.</i> Ag/AgCl	0.1 M NaOH	183
Cu/Cu ₂ O hollow microspheres	33.63	0.22–10.89	0.05	+0.45 <i>vs.</i> SCE	0.1 M NaOH	108
Cu/CuO nanowires	—	0.1–12	50	+0.3 <i>vs.</i> SCE	0.1 M NaOH	109
Pd/CuO nanofibers	1061	0.2–2.5	0.019	+0.32 <i>vs.</i> SCE	0.1 M NaOH	185
TiO ₂ /CuO nanotube arrays	79.79	Up to 2.0	1	+0.5 <i>vs.</i> SCE	0.1 M NaOH	105
CdO/NiO nanofibers	212.71	Up to 6.37	0.35	+0.6 <i>vs.</i> Ag/AgCl	0.1 M NaOH	123

followed by anodic oxygen transfer and formation of oxidized organic compound intermediate.

Zhao *et al.*¹⁹³ has reported a nanocrystalline BDD electrode, which showed high sensitivity, low detection limit, good selectivity and large linear range toward the non-enzymatic glucose detection in sodium hydroxide solution. Similar to the BDD electrode reported by Lee, the nanocrystalline BDD electrode also underwent hydrogen flame treatment to prevent the formation of carboxyl functionalities at high anodic potentials that decrease the conductivity of BDD electrode. Although the quench of glucose signals were observed at BDD electrode and microcrystalline BDD electrode after acid treatment, the nanocrystalline BDD electrode could still maintain a good amperometric response for glucose after 30 min treatment by aqua regia. This interesting observation indicates the surface morphology with regards to the diamond dimension, grain boundaries and boron atoms distribution could strongly affect the electrochemical activity of BDD electrode.

The above proposition is further supported by a recent work by Luo *et al.*,¹⁹⁴ who fabricated boron-doped diamond nanoforest (BDDNF) for the non-enzymatic detection of glucose. Compared to plane BDD, BDDNF exhibited well-defined current response and significantly improved sensitivity. The electrode also showed well distinguished peaks of AA, UA and glucose, which respond at 0.1, 0.3 and 0.6 V, respectively.

Despite the enhanced sensitivity by tailoring the nanostructure of BDD, the linear range of glucose sensors in all three publications are not above 10 mM, which is the major limitation for their practical usage. In addition, the sensitivities of these electrodes are also lower than some metal modified BDD electrodes. For example, nickel nanoparticles modified BDD achieved a sensitivity of $101.9 \mu\text{A mM}^{-1} \text{cm}^{-2}$,⁸¹ while the value of BDDNF is only $8.1 \mu\text{A mM}^{-1} \text{cm}^{-2}$. However, nanocrystalline and nanostructured BDD electrodes still hold great potential for the development of viable and reusable glucose biosensors.

2.4.2 Carbon nanotubes. In the last decade, carbon nanotubes (CNTs) have been intensively studied to improve the performance of first and second generation glucose biosensors.^{196–201} They are also reported to facilitate the direct electron transfer of GOx and used to develop third-generation glucose sensors.^{202–204} In addition, both MWCNTs and SWCNTs have demonstrated their capability for non-enzymatic glucose detection,^{205,206} but most often CNTs are used as support for other electrocatalysts.^{70,71,94,113,117,124,127,136,207,208}

The first CNTs-based non-enzymatic glucose sensor was based on well aligned MWCNTs grown on tantalum substrate, as reported by Ye *et al.*²⁰⁵ The electrode showed a high sensitivity for glucose oxidation at low overpotential of +0.2 V (*vs.* Ag/AgCl) in 0.1 M NaOH, with a large linear range up to 11 mM. In addition, the MWCNTs-based non-enzymatic glucose sensor exhibited reproducible current response for glucose in the presence of high concentration of chloride ions, indicating excellent anti-poisoning property of the electrode. However, the interferential species such as AA and UA had a significant impact on glucose detection, possibly due to the overlapped oxidation potentials of these species with glucose. SWCNTs-

based non-enzymatic glucose biosensor has been reported by Wang *et al.*,²⁰⁶ who fabricated freestanding SWCNTs films with large area which were bound to the glass surface by Nafion. The SWCNTs film electrode showed direct oxidation of glucose in alkaline solution at the potential of 0.5 V (*vs.* Ag/AgCl), and exhibited a fast response less than 10 s to glucose even in the presence of 0.2 M chloride ions. The fabricated biosensor achieved a reproducible high sensitivity of $248.6 \mu\text{A mM}^{-1} \text{cm}^{-2}$, which is significantly larger than the value of MWCNTs based electrode, *ca.* $4.36 \mu\text{A mM}^{-1} \text{cm}^{-2}$. However, the linear range of SWCNTs film electrode was limited up to 2.16 mM.

The non-enzymatic glucose biosensors based on CNTs decorated with various other electrocatalysts including metallic nanoparticles, metal oxides, and alloys have been already discussed in the previous sections, which are not repeated here.

2.4.3 Graphene and other carbon nanomaterials. Graphene, a single atom layer of sp^2 hybridized carbon, has attracted tremendous research interest since its discovery in 2004 by Novoselov *et al.*²⁰⁹ Due to its unusual mechanical strength, ultralarge specific surface area and extraordinary electrical properties, graphene has been intensively studied and employed for fabrication of enzymatic glucose biosensors.²¹⁰ However, graphene based non-enzymatic glucose biosensor has not been reported until very recently. Mallesha *et al.*²¹¹ claimed that functionalized graphene modified graphite electrode (FGGE) could be used for enzymeless determination of glucose in alkaline solution. The glucose was oxidized at +400 mV (*vs.* SCE) on FGGE, and the biosensor achieved a sensitivity of $28.4 \mu\text{A mM cm}^{-2}$, with a linear range of 0.5–7.5 mM and a detection limit of 10 μM . Other non-enzymatic glucose biosensors based on graphene hybrid materials^{47,60,98,159} have been discussed previously.

Carbon nanofibers (CNFs) are another class of carbon nanomaterials which find many interesting applications in chemical and biosensors. CNFs comprise of well-arranged graphite layers organized into cylindrical structures. Unlike CNTs, CNFs are not hollow in the core. In addition, they expose the edge plane rather than the basal plane of graphene on their surfaces, which provide them with very large surface area and extremely high conductivity.²¹² Non-enzymatic glucose biosensors based on CNFs have been reported recently. For example, Rathod *et al.*²¹³ investigated the electrocatalytic performance of CNFs/Pt NPs toward the glucose oxidation under physiological pH conditions. Liu *et al.*⁷⁷ developed a non-enzymatic glucose biosensor based on CNFs/Ni NPs, which exhibited a high sensitivity of $420.4 \mu\text{A mM}^{-1} \text{cm}^{-2}$ with a wide linear range of 2 μM –2.5 mM.

3 Conclusions and future prospects

Nanomaterials based non-enzymatic glucose biosensors have been continuously and increasingly reported in recent years. With the help of nanotechnology, many problems associated with non-enzymatic glucose sensors have been alleviated or solved. For example, the surface poisoning of Pt electrode by

chloride ions was successfully solved by nanoporous Pt electrode and PtPb nanoparticle alloy modified electrode. In addition, some nanostructured catalysts could significantly reduce the overpotential for glucose oxidation, which effectively avoided the interferences by electroactive species in the blood. More importantly, the sensitivity of non-enzymatic glucose sensor is significantly improved by nanomaterials modified electrode, which usually achieved a value of more than $100 \mu\text{A mM}^{-1} \text{cm}^{-2}$. The sensitivity is considerably higher than those of non-enzymatic glucose sensors based bulk electrode or most enzymatic glucose biosensors, which are usually less than $10 \mu\text{A mM}^{-1} \text{cm}^{-2}$. Nevertheless, the major obstacle that prevents many non-enzymatic glucose biosensors working in human blood is that they are not able to catalyse the glucose oxidation under physiological conditions. This is especially the case for Ni, Cu, metal oxide and carbon nanomaterials based electrodes, in spite of their extraordinarily high sensitivity achieved. The most promising non-enzymatic glucose sensors should be nanoporous Pt electrode and Pt based alloys modified electrode, since they not only effectively resist the surface fouling by chloride ions and avoid the various interferences, but also allow the catalysis of glucose in neural pH solution. The major concern of non-enzymatic electrodes toward commercialization would be the fabrication cost. In addition to blood glucose sensing, nanomaterials based non-enzymatic glucose sensors may also find extensive applications in bioindustrial process monitoring due to their sterilization compatibility. Besides oxygen and pH, we might also be able to monitor the glucose level in a fermentation plant or bioreactor in real time manner. Furthermore, although some non-enzymatic glucose catalysts are not applicable for blood glucose monitoring, they are well suited for application in glucose fuel cells which do not require physiological conditions. In contrast to enzymatic systems which could merely oxidize glucose to gluconolactone, many nanostructured non-enzymatic electrocatalysts are capable to oxidize glucose completely to CO_2 and H_2O at low potentials, significantly enhancing the energy conversion efficiency. With new inspirations suggested by novel characteristics of nanostructured materials and vast opportunities brought by nanotechnology to innovative non-enzymatic glucose biosensors, it is reasonable to expect the significant advances that revolutionize the glucose biosensor industry in the near future.

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