

Recent advances in electrochemical sensing for hydrogen peroxide: a review†

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Due to the significance of hydrogen peroxide (H_2O_2) in biological systems and its practical applications, the development of efficient electrochemical H_2O_2 sensors holds a special attraction for researchers. Various materials such as Prussian blue (PB), heme proteins, carbon nanotubes (CNTs) and transition metals have been applied to the construction of H_2O_2 sensors. In this article, the electrocatalytic H_2O_2 determinations are mainly focused on because they can provide a superior sensing performance over non-electrocatalytic ones. The synergetic effect between nanotechnology and electrochemical H_2O_2 determination is also highlighted in various aspects. In addition, some recent progress for *in vivo* H_2O_2 measurements is also presented. Finally, the future prospects for more efficient H_2O_2 sensing are discussed.

1. Introduction

Hydrogen peroxide (H_2O_2) is a very simple compound in nature but with great importance in pharmaceutical, clinical, environmental, mining, textile and food manufacturing applications.¹ In living organisms, besides its well-known cytotoxic effects, H_2O_2 also plays an essential role as a signalling molecule in regulating diverse biological processes such as immune cell activation, vascular remodelling, apoptosis, stomatal closure and root growth.^{2–4} H_2O_2 is also a side product generated from some classic biochemical reactions catalyzed by enzymes such as glucose oxidase (GOx), alcohol oxidase (AOx), lactate oxidase (LOx), urate oxidase (UOx), cholesterol oxidase (ChoOx), α -amino acid oxidase (DAOO), glutamate oxidase (GLOx), lysine oxidase (LyOx), oxalate oxidase (OxaOx), etc. Therefore, the study on H_2O_2 detection is of practical significance for both academic and industrial purposes. Conventional techniques for hydrogen peroxide determination such as fluorimetry,⁵ chemiluminescence,⁶ fluorescence⁷ and spectrophotometry⁸ are complex, costly and time consuming. In comparison, electrochemistry can offer simple, rapid, sensitive, and cost effective means since H_2O_2 is an electroactive molecule.⁹

In electrochemistry, H_2O_2 can be either oxidized or reduced directly at ordinary solid electrodes. However, these processes in analytical applications are limited by slow electrode kinetics and

high overpotential which will downgrade the sensing performance and may incur large interferences from other existing electroactive species in real samples such as ascorbate, urate, bilirubin, etc. Thus, the current research on H_2O_2 detection is mainly focused on electrode modifications in order to decrease the overpotential and increase the electron transfer kinetics. For these considerations, a large range of materials such as redox proteins, dyes, transition metals, metal oxides, metal phthalocyanines, metal porphyrins, redox polymers, and carbon nanotubes have been employed to conduct electrocatalytic H_2O_2 detection. On the other hand, in recent years, nanomaterials have attracted tremendous research interest because of their desirable chemical, physical and electronic properties that are different from those of bulk materials. Furthermore, the size and structure of nanomaterials can be tailored for designing a novel sensing platform and enhancing sensing performance.¹⁰ Herein, some of the above-mentioned materials tailored into or combined with nanomaterials have shown distinct advantages over conventional materials for H_2O_2 sensing.^{11–13} The aim of this review is to summarize the recent advances since 2000 and gain an insight into the materials used in the electrocatalytic sensing of H_2O_2 .

2. Materials used for electrocatalytic hydrogen peroxide sensing

2.1. Metal hexacyanoferrates

2.1.1. Ferric hexacyanoferrate. Ferric hexacyanoferrate or Prussian blue (PB) has been denoted as an “artificial peroxidase” because the reduced form of PB—Prussian white—is capable of catalyzing the reduction of H_2O_2 at low potentials (−50 mV (vs. Ag/AgCl)) like peroxidases.^{14,15} PB also owns good catalytic specificity to H_2O_2 due to the polycrystal structure of PB which may allow penetration of only small molecules into its lattice while larger molecules such as ascorbic acid (AA), uric acid

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(UA), and *para*-acetylaminophenol (APAP) are excluded.¹⁶ Therefore, PB or PB-based composites have been intensively studied and widely used in biosensor constructions.^{14,17,18} The most straightforward use of PB in H₂O₂ sensing is to electrochemically coat the working electrode surface with a PB layer followed by overlaying additional layers which may be used for loading enzyme, stabilizing PB, improving selectivity, *etc.* Various oxidases including GOx,^{19–21} choline oxidase (ChOx),^{22,23} ChoOx,²⁴ ALOx,²⁵ galactose oxidase (GaOx),²⁶ GLOx,²⁷ LOx,²⁸ LyOx,^{29,30} OxaOx³¹ and xanthine oxidase (XOx)³² have been combined with PB for biosensor construction. Screen printing technology was also employed to fabricate PB based sensors. O'Halloran *et al.*³³ made the bulk modification of the carbon ink by PB microparticles (<38 µm) and Mattos *et al.*³⁴ modified Au and Pt screen-printed electrodes with electrochemically deposited PB. Ricci *et al.*²³ modified the graphite ink based screen printed electrode surfaces with *in situ* chemically synthesized PB and found the enhanced life-time and pH stability of resulted sensors.

With the attractive advantages from nanotechnologies, PB based H₂O₂ sensing has been developed with nanomaterials. Li *et al.*³⁵ constructed an amperometric biosensor *via* grafting PB nanoparticles on the polymeric matrix of multiwalled carbon nanotubes (MWCNTs) and poly(4-vinylpyridine) (PVP). The MWCNT/PVP/PB composite films were fabricated by casting films of MWCNTs wrapped with PVP on gold electrodes followed by electrochemical deposition of PB on the MWCNT/PVP matrix. This modified electrode shows largely enhanced sensitivity of 1.3 µA µM^{–1} cm^{–2} and a detection limit of 25 nM due to the remarkable synergistic effect of MWCNTs and PB. Li *et al.*³⁶ deposited PB on the MWCNT modified pyrolytic graphite electrode and found improved electrochemical stability over a wide pH range and larger response to the reduction of hydrogen peroxide compared to a PB modified pyrolytic graphite electrode. One-step electroless depositions of PB nanoparticles on CNTs were carried out by dispersing CNTs in a mixture of Fe³⁺, [Fe(CN)₆]^{3–} and KCl.^{37,38} The driving forces for CNT assisted PB nanoparticle synthesis are due to the difference in the redox potentials between CNTs and Fe³⁺/Fe²⁺ and between CNTs and [Fe(CN)₆]^{3–}/[Fe(CN)₆]^{4–}. Later, Du *et al.*³⁹ fabricated a porous PB–MWCNT film by the electrochemical co-deposition method. The characterization showed that this PB–MWCNT composite film gave a larger response current to the reduction of H₂O₂ with a sensitivity of 856 µA mM^{–1} cm^{–2} and a detection limit of 23 nM. PB has also been electrodeposited on a graphene oxide modified glassy carbon electrode for fabricating a glucose sensor and this graphene oxide/PB hybrid based sensor showed a largely enhanced response to H₂O₂.^{40,41} PB itself can also be tailored into different nanostructures for sensor constructions. Liu *et al.*⁴² synthesized PB nanoparticles (*ca.* 50 nm) self-assembled onto a gold electrode using cysteine as a bridge between the gold surface and the nanoparticles. Zhang *et al.*⁴³ constructed multi-PB nanocluster/enzyme-immobilized poly (toluidine blue) layers by depositing PB and polymerizing toluidine blue alternately from an acidic solution of ferricyanide. Later, Zhao *et al.*⁴⁴ used a layer by layer assembly method to construct multi-PB nanoparticle/enzyme-immobilized polymer layers. A bilayer of poly(diallyldimethylammonium chloride) (PDDA) and poly(sodium 4-styrenesulfonate) (PSS) is

consecutively adsorbed on 3-mercaptop-1-propanesulfonic acid modified Au electrode surfaces, forming stable, ultrathin multi-layer films. Subsequently, PDDA protected PB nanoparticles and negatively charged glucose oxidase are consecutively adsorbed onto the PSS-terminated bilayer. This process allows the fabrication of sensing membranes with controlled thickness, structural morphology and biocatalyst loading. The template synthesized PB nanostructures were also achieved by depositing PB in lyotropic liquid crystalline templates⁴⁵ and highly ordered porous anodic alumina (PAA) membrane,⁴⁶ respectively. Both results demonstrated enhanced sensing performances in comparison with conventional PB based electrodes.

The major drawback of PB in sensing applications is the lack of operational stability in neutral and alkaline solutions because the reduced form of PB, Prussian white, can be dissolved by hydroxide ions.^{16,47} Therefore, it is necessary to improve the stability of PB at relatively high pH. Fortunately, some studies demonstrated that surfactants including cetyltrimethylammonium bromide (CTAB), polyvinyl alcohol, polyvinyl pyrrolidone, polyallylamine hydrochloride, polydiallyldimethylammonium chloride, tetrabutylammonium toluene-4-sulfonate and polystyrene sulfonate can effectively enhance the electrochemical stability of metal hexacyanoferrate.^{27,48–56}

2.1.2. Other metal hexacyanoferrates. After the discovery of the electroactivity of PB, other metal hexacyanoferrates including copper,^{57–61} nickel,^{58,62–65} cobalt,^{58,66–69} chromium,^{70,71} vanadium,¹ ruthenium^{72,73} and manganese⁷⁴ hexacyanoferrates have been also investigated for hydrogen peroxide sensing. In comparison with PB based electrodes, these metal hexacyanoferrate based sensors have a similar or lower capability of electrocatalytic reduction for H₂O₂, but with more electrochemical stabilities over a wide range of pH.^{18,57,74} This advantage is taken into account because it permits the better sensing operation at physiological pHs which are favoured by enzymes. Another advantage is that metal hexacyanoferrates can perform well in solution containing not only potassium but also other alkali metal cations such as lithium, sodium, rubidium or caesium, contrary to PB that only shows good electroactivity in K⁺ containing electrolytes.^{75–78}

2.2. Heme proteins

Heme proteins such as horseradish peroxidase (HRP), catalase (CAT), cytochrome c (Cyt c), hemoglobin (Hb), microperoxidase (MP) and myoglobin (Mb) are a category of metalloproteins containing iron centered porphyrin as their prosthetic groups. This iron in the heme can easily undergo oxidation and reduction over a wide range of potentials which are varied by the protein environment around heme groups.^{79,80} Due to the redox capability of heme proteins, they have the great potential to be used in bioelectrochemical applications, especially biosensors. The most efficient practice for fabricating redox protein based electrochemical biosensors is to establish direct electron transfer between the protein and electrode (the third generation biosensor). The biosensors based on this configuration can offer better selectivity since they are able to operate in a potential range closer to the redox potential of the protein itself, thus

giving less exposure to interfering reactions, unlike the redox mediator based ones (the second generation biosensor) that facilitate not only the electron transfer between the electrode and enzyme but also various interfering reactions.^{81,82} The main challenge to construct the third generation biosensor is to optimize the electron transfer between the heme protein and electrode, because the prosthetic group of heme protein is shielded by the polypeptides, which make the electron transfer distance so long that the tunnelling mechanism rarely happens.⁸² Thus, a careful design of the biosensor architectures is essential for facilitating direct electron transfer in predefined pathways interconnecting the active centre and the electrode surface.⁸³ Various strategies such as silica sol-gel,⁸⁴ conducting polymer,^{85,86} ionic liquid,⁸⁷⁻⁸⁹ self-assembly monolayer⁹⁰ and layer-by-layer assembly^{91,92} have been successfully proved effective in building the third generation hydrogen peroxide sensor. Furthermore, with the attractive advantages, more and more nanomaterials have been integrated with heme proteins to construct direct electron transfer based hydrogen peroxide sensors. Table 1 shows the part of recently published heme proteins and nanomaterials based third generation biosensors and their performances.

Though HRP, Hb, CAT, Mb and Cyt c have been used to successfully construct the third generation biosensors, respectively, their differences in direct electrochemistry still remain. Lotzbeyer *et al.*¹²⁰ made early investigations on the direct electron transfer capability of HRP, Cyt c, Mb, microperoxidase MP-11 and haemin all of which can catalyze the reduction of hydrogen peroxide. These heme proteins were covalently

tethered to self-assembled monolayers on the gold surface. As direct electron transfer processes are predominantly limited by the distance between the active site of the protein and the electrode surface, the highest electrocatalytic efficiency was observed for the smallest heme proteins (*e.g.* microperoxidase MP-11, haemin). Although haemin exhibits a 3300 fold lower catalytic activity for hydrogen peroxide reduction in solution in comparison with HRP, it showed a more than 10 fold higher electrocatalytic activity when immobilized at the monolayer. This tremendous difference could be attributed to a higher surface concentration for the smaller proteins, the improved access for the substrate to their active sites and the increased electron-transfer rate due to the decrease of the distance between the redox site and electrode surface. Wu *et al.*¹²¹ studied the catalysis of Mb, Hb, HRP and CAT in the silk fibroin film on graphite electrodes with direct electrochemistry. At a potential of -0.2 V (vs. SCE), at which the reduction of heme Fe(III) does not interfere, the current was monitored with consecutive H_2O_2 injection. The result showed that the HRP based electrode possesses the highest sensitivity followed by the CAT modified electrode. Li *et al.*¹²² investigated the direct electron transfer reaction of HRP and CAT immobilized by methyl cellulose and found that the HRP based electrode showed about 5 fold higher sensitivity to H_2O_2 than the CAT based electrode. Peng *et al.*¹²³ fabricated a magnetic core-shell $\text{Fe}_3\text{O}_4@\text{Al}_2\text{O}_3$ nanoparticle attached magnetic glassy carbon electrode for the immobilization of heme proteins including Hb, Mb and HRP. The direct electrochemistry of Hb, Mb and HRP was observed and their apparent Michaelis-Menten constants (K_M^{app}) for hydrogen

Table 1 Examples of heme proteins and nanomaterials based third generation biosensors for H_2O_2

Heme proteins	Nanomaterials	Linear range/ μM	Detection limit/ μM	References
HRP	Au nanoparticles	$41-6.3 \times 10^2$ $0.5-5.2 \times 10^3$ $15-1.1 \times 10^3$	5.9 0.1 9.0	93 94 95
	Au nanowire array	$0.74-1.5 \times 10^4$	0.42	96
	TiO_2 nanotube	$0.5-10$ and $50-1.0 \times 10^3$	0.1	97
	Graphene	$3.5-3.29 \times 10^2$ 0.33-14.0	1.17 0.11	98 99
	CNTs	$0.6-1.8 \times 10^3$ 1.07-48.4 $5.0-1.05 \times 10^3$ $86-1.0 \times 10^4$	0.3 0.357 0.5 86	100 101 102 103
	CNTs	Up to 0.1	10	104
	Au nanoparticles	$10-1 \times 10^2$ $0.3-6 \times 10^2$ $1 \times 10^3-5 \times 10^3$	1 0.05 —	105 106 107
	NiO nanoparticles	$1-1 \times 10^3$	—	108
	Au nanoparticles	$8.5 \times 10^2-1.3 \times 10^4$ $50-1.15 \times 10^3$ $10-1.2 \times 10^4$ $2-3.0 \times 10^2$	9.8 3 6.3 0.5	109 110 111 112
	ZnO nanosheets	$1-1 \times 10^3$	0.8	113
Hb	CNTs	$23.6-1.34 \times 10^2$	7.87	101
	Au nanoparticles	$7.4 \times 10^2-1.3 \times 10^4$ $6 \times 10^2-1.7 \times 10^3$ and $2 \times 10^3-2.2 \times 10^4$	6.4 —	109 114
Mb	Pt nanoparticles	0.44-44	2.8×10^{-2}	115
	CdTe nanoparticles	$7.44-6.95 \times 10^2$	2.23	116
	TiO_2 nanorods	$0-1.02 \times 10^2$	0.72	117
	CNTs	$24.2-1.67 \times 10^2$	8.07	101
	Au nanoparticles	$1.3 \times 10^3-1.3 \times 10^4$ $0.1-2.35 \times 10^2$	1.8 —	109 118
	Nanoporous ZnO	$4.8-2.0 \times 10^2$	2.0	119

peroxide reduction were calculated as 0.12 mM, 0.105 mM and 0.083 mM, respectively. This result suggested that the HRP based electrode has the highest affinity to H_2O_2 among the three heme protein based electrodes. Wang *et al.*¹²⁴ investigated the effects of 1-butyl-3-methylimidazolium tetrafluoroborate ($[\text{bmim}][\text{BF}_4]$) on direct electrochemistry and bioelectrocatalysis of Hb, Mb and CAT entrapped in agarose hydrogel films. The $K_{\text{M}}^{\text{app}}$ of CAT, Hb, and Mb based electrodes for H_2O_2 reduction was 0.317 mM, 0.755 mM and 0.593 mM, respectively, and the slope of the calibration curves of CAT, Hb, and Mb based electrodes for H_2O_2 detection was 2.17 mA M^{-1} , 0.24 mA M^{-1} and 0.996 mA M^{-1} . All the constants and the slopes indicated that the CAT based electrode has the highest affinity and best sensitivity over Hb and Mb based electrodes for H_2O_2 determination. Later, Wang *et al.*¹⁰¹ studied direct electrochemistry and electrocatalysis of heme proteins including Hb, Mb and HRP immobilized in SWCNT-CTAB nanocomposite film modified electrodes. The electrocatalytic reduction of H_2O_2 on these heme protein based electrodes was investigated by amperometry with an applied potential of -0.4 V . The result showed the slope of the calibration curve of HRP, Hb and Mb was $0.133 \mu\text{A } \mu\text{M}^{-1}$, $0.112 \mu\text{A } \mu\text{M}^{-1}$ and $0.094 \mu\text{A } \mu\text{M}^{-1}$, respectively, which suggested that the HRP modified electrode gave the best performance over Hb and Mb based electrodes on H_2O_2 determination. The same results were also achieved on HRP, Hb and Mb immobilized Au nanoparticle-bacteria cellulose nanofiber modified electrodes by Wang *et al.*¹²⁵

2.3. CNTs and graphene

2.3.1. CNTs. CNTs have been widely used for chemical and biological sensing applications due to their high surface area, high electric conductivity, ability to accumulate analyte, alleviation of surface fouling, capability to make surface functionalization and electrocatalytic activity.^{126,127} Studies have shown that CNTs can electrocatalyze both the oxidation and reduction of H_2O_2 . Wang's group fabricated CNT/Nafion modified electrodes¹²⁸ and CNT/Teflon modified electrodes¹²⁹ based on the dispersion of MWCNTs within Nafion and Teflon as binders, respectively. Significant oxidation and reduction currents around $+0.20 \text{ V}$ (*vs.* Ag/AgCl) for H_2O_2 were observed on both sensor constructions. The performance of the MWCNT/Teflon/GOx electrodes operated at the potentials of $+0.6 \text{ V}$ and $+0.1 \text{ V}$ (*vs.* Ag/AgCl) was studied. It was found that low-potential operation results in a highly linear response (over 2–20 mM range), high selectivity and a slower response time ($\sim 1 \text{ min}$ *vs.* 25 s at $+0.6 \text{ V}$) (*vs.* Ag/AgCl). Despite the absence of permselective coating, the sensor response operated at $+0.1 \text{ V}$ (*vs.* Ag/AgCl) was not affected by the addition of APAP and UA.¹²⁹ Manesh *et al.*¹³⁰ reported a nanofibrous glucose electrode fabricated by the immobilization of GOx into an electrospun composite membrane consisting of polymethylmethacrylate (PMMA) dispersed with multiwall carbon nanotubes wrapped by a cationic polymer PDDA. This modified electrode recorded significant electrocatalysis for the oxidation and reduction of H_2O_2 around 0 mV. The operation potential of this electrode was also at $+0.1 \text{ V}$ (*vs.* Ag/AgCl) for H_2O_2 oxidation. Nafion was necessary to eliminate the interferences from UA and AA in this study. Kachoosangi *et al.*¹³¹ fabricated CNT/ionic liquid *n*-

octylpyridinium hexafluorophosphate (OPFP) composite based sensors and found that this configuration showed overwhelming performance over the CNT/mineral oil composite based electrode due to the excellent charge transfer properties and extremely low capacitance of this ion liquid. CNTs dispersed in mineral oil,¹³² polyaniline (PANI),^{133,134} polypyrrole (PPy),¹³⁵ poly(vinyl alcohol) (PVA),¹³⁶ poly(pyrocatechol violet) (poly-PCV),¹³⁷ poly(3,4-ethylenedioxythiophene) (PEDOT),¹³⁸ chitosan^{139–142} and nano- Fe_3O_4 ¹⁴³ (for magnetic loading) have also shown good electrocatalysis to H_2O_2 . Interestingly, Gomathi *et al.*¹⁴⁴ reported that MWCNT/chitosan nanocomposite modified electrodes were operated based on the oxidation of H_2O_2 at 0.34 V (*vs.* Ag/AgCl). Without a permselective membrane at such a potential, the sensor exhibited no interferences from AA, UA and APAP. Rivas' group studied the electrochemical behaviour of MWCNTs dispersed in polyethylenimine (PEI).¹⁴⁵ This PEI/CNT modified electrode showed an excellent electrocatalytic activity toward H_2O_2 because it was found that the overpotentials for the oxidation and reduction of hydrogen peroxide were decreased by 350 mV and 450 mV, respectively, and the currents were also higher than those obtained with other dispersant agents like Nafion, concentrated acids or chitosan. Besides the traditional dispersion, Lin *et al.*¹⁴⁶ developed glucose biosensors based on a CNT nanoelectrode array grown from Ni nanoparticles on a Cr-coated Si substrate. This sensor array was operated at -0.2 V (*vs.* Ag/AgCl) with good selectivity against the interferences from AA, UA, and AC.

To get further insight into the electrocatalysis of CNT to H_2O_2 , Xu *et al.*¹⁴⁷ compared the nitrogen-doped carbon nanotubes (NCNTs) with MWCNTs. CNTs doped with N can yield a large number of defective sites on nanotube surfaces and have been proved to have largely improved electrocatalysis.¹⁴⁸ In this study, the NCNTs exhibited greatly enhanced electrocatalytic activity toward the oxidation and reduction of H_2O_2 at $+0.25 \text{ V}$ and -0.1 V (*vs.* Ag/AgCl), respectively. Compton's group reported a very interesting finding on the electrocatalytic activity of MWCNTs.¹⁴⁹ By comparing the electrochemical behaviour of Fe(III) oxide modified basal plane pyrolytic graphite (BPPG) electrode and CNT modified BPPG electrode in H_2O_2 solution, they found that the electrocatalysis was due to iron oxide particles arising from the chemical vapor deposition nanotube fabrication process rather than due to intrinsic catalysis attributable to the carbon nanotubes arising, for example, from edge plane-like sites/defects.

2.3.2. Graphene. Graphene has attracted considerable attention from both scientific and technological communities due to its unique physicochemical properties and various potential applications in recent years.¹⁵⁰ In comparison with CNTs, graphene shows competitive advantages of low cost, ease of processing and safety.¹⁵¹ Graphene is also an ideal platform for electrochemical research since it is free from the contamination of transition metals which are apt to exist in CNTs. Zhou *et al.*¹⁵² characterized a chemically reduced graphene oxide (CR-GO) modified electrode which shows the much lower onset potential of H_2O_2 oxidation/reduction started at $0.2/0.1 \text{ V}$ (*vs.* Ag/AgCl) than those of the graphite electrode and bare electrode. The superior electrocatalytic activity of CR-GO is most likely attributed to the high density of edge-plane-like defective sites on

CR-GO.^{153–155} Niu's group characterized a PVP-protected graphene/polyethylenimine functionalized ionic liquid (PFIL) electrode for H₂O₂ electrocatalysis.¹⁵⁶ The more positive reduction potential (onset potential at ~ 0 V) and more obvious reduction current indicated that the graphene-based modified electrode had much better electrocatalysis toward H₂O₂ than the PFIL modified electrode. Later, the same group combined both graphene and gold nanoparticles (AuNPs) dispersed in chitosan to make a glucose biosensor.¹⁵⁷ This modified electrode exhibited the highest electrocatalytic activity toward H₂O₂ than the graphene/chitosan, AuNPs/chitosan, and chitosan modified electrodes. This electrocatalysis enhancement might be attributed to the synergistic effect of graphene and AuNPs.¹⁵⁸

2.4. Metals and metal oxides

2.4.1. Metals. Transition metals and their compounds are known as good catalysts either because of their ability to adopt multiple oxidation states or, in the case of the metals, to adsorb other substances onto their surface and activate them in the process. On the other hand, nano-sized metals can display unique advantages of enhanced mass transport, high effective surface area, size controlled electrical, chemical and optical properties and effective utilization of expensive materials.¹³ Thus, transition metal nanoparticles can be made excellent catalysts due to their high ratio of surface atoms with free valences to the cluster of total atoms.¹⁵⁹ A wide range of transition metals including platinum (Pt),¹⁶⁰ palladium (Pd),¹⁶⁰ copper (Cu),^{161–163} rhodium (Rh),^{79,80} iridium (Ir)^{79,163–165} and ferrum (Fe)¹⁶⁶ have been successfully used for electrocatalyzed H₂O₂ determination. As one of the most intensively studied transition metals, various Au nanomaterials with different shapes and structures such as Au nanowire assembling architecture,¹⁶⁷ nanoporous Au,¹⁶⁸ Au nanocages¹¹ and Au nanoparticles¹⁶⁹ have been investigated for electrocatalytic H₂O₂ reduction. It seems that Au nanocage¹¹ and nanoporous Au¹⁶⁸ slightly outperformed others.

To achieve high loading and reserving high catalytic activities for transition metal nanoparticles, carbon based nanomaterials especially CNTs were extensively utilized as supporting substrates due to their high surface area, high conductivity and high electrocatalytic activity. After the first report of Pt nanoparticle/CNT as a sensing platform,¹⁵⁹ numerous studies have been conducted based on this strategy for H₂O₂ sensing though the approaches may slightly vary.^{170–175} Other transition metal nanoparticles such as Pd nanoparticles¹⁷⁶ and Ag nanoparticles^{177,178} also have been utilized with CNTs for electrocatalytic H₂O₂ sensing. Furthermore, besides the most used CNTs, graphene,^{103,179,180} graphite nanoplatelet,¹³ carbon nanofiber,^{181,182} silicon nanowire,¹⁸³ and Au nanowire array¹⁸⁴ were also proved to be suitable nanostructural substrates for various transition metal nanoparticles.

In recent years, bimetallic alloy nanoparticles have attracted considerable attention because they have both the favourable catalytic properties over monometallic counterparts and unique advantages from nanomaterials. Xiao *et al.*¹⁸⁵ fabricated AuPt nanoparticles on chitosan-ionic liquid (trihexyltin-tradecylphosphonium bis(trifluoromethylsulfonyl)imide ($[P(C_6)_3C_{14}][Tf_2N]$)) film by using an ultrasonic electrodeposition method. Chitosan acted as an adsorbent for the metal ions, and

$[P(C_6)_3C_{14}][Tf_2N]$ played a dual role of matrix and stabilizer in the formation of the nanoparticles. By comparing the electrochemical response of different modified electrodes toward H₂O₂ reduction, the AuPt-chitosan- $[P(C_6)_3C_{14}][Tf_2N]$ modified electrode exhibits the lowest overpotential. This synergistic effect can be attributed to the presence of Au that can reduce the strength of Pt-OH formation.^{186,187} Furthermore, this sensor was operated at a low working potential (-0.05 V *vs.* Ag/AgCl) with a sensitivity of 3.98 mA mM⁻¹ cm⁻², a detection limit of 0.3 nM in a linear range of 5 – 355 nM and a very high selectivity of less than 5% decrease of the 20 nM H₂O₂ signal with the existence of a bunch of foreign species. Later, Safavi and Farjam¹⁸⁸ used the same strategy to construct a cholesterol biosensor based on a AuPt-Ch-IL modified electrode and also achieved good performance for H₂O₂ determination. Li *et al.*¹⁸⁹ utilized AuPt alloy nanoparticles deposited on MWCNTs to fabricate an H₂O₂ based amperometric immunosensor in which AuPt alloy nanoparticles not only could be used to assemble biomolecules with well maintained bioactivity, but also could facilitate the shuttle of electrons. Liu *et al.*¹⁹⁰ reported an amorphous ternary FeNiPt nanomaterial with tunable length to construct an electrochemical sensing platform. The FeNiPt nanorods with large axial ratio exhibit enhanced electrocatalytic activity towards both the oxidation and reduction of H₂O₂. H₂O₂ is cathodically determined on FeNiPt-nanorod modified glassy carbon electrodes with relatively high selectivity at the appropriate potential of 0 V (*vs.* Ag/AgCl). The anodic H₂O₂ detection based on the same electrode showed a sensitivity of 2.45 mA mM⁻¹ cm⁻², which is 4-fold higher than that of the cathodic detection and those Pt nanoparticle-based H₂O₂ determination, and the detection limit of 40 nM with a dynamic linear range from 100 nM to 30 mM, which is wider than Pt nanoparticles and binary Pt alloys based detection.

2.4.2. Metal oxides. Some transition metal oxides such as manganese oxide,^{163,191–198} cobalt oxide,¹⁹⁹ titanium dioxide,²⁰⁰ copper oxide^{201,202} and iridium oxide²⁰³ have been reported to show electrocatalytic activity to H₂O₂. However, many of them were based on the electrocatalytic oxidation of H₂O₂ in which high potentials were applied on the working electrode. For example, MnO₂ nanoparticle and dihexadecyl hydrogen phosphate composite film modified electrode was used for H₂O₂ determination at an applied potential of $+0.65$ V (*vs.* saturated calomel electrode (SCE))¹⁹² and a TiO₂/MWCNT modified electrode was employed to detect H₂O₂ at an applied potential of $+0.4$ V (*vs.* Ag/AgCl).²⁰⁰ From the application point of view, the operation potentials of these sensors are too high to be applied to real biological samples. Xu *et al.*¹⁹⁸ reported the MnO₂/MWCNT modified electrode for H₂O₂ determination which showed high anti-interference property without any permselective membranes against AA, citric acid and UA in spite of the high operation potential of 0.45 V (*vs.* Ag/AgCl). Bai *et al.*²⁰⁴ found that MnO₂ nanoparticle modified electrodes show bi-direction electrocatalytic ability toward the reduction/oxidation of H₂O₂. When this modified electrode was operated at 0 V (*vs.* Ag/AgCl) in the H₂O₂ reduction pathway, the interference from AA was greatly depressed. Copper oxide seems a more suitable material for H₂O₂ sensing. Luque *et al.*²⁰² reported that the CuO/carbon paste electrode showed an excellent electrocatalytic activity towards the

oxidation and reduction of H_2O_2 . This modified electrode was operated at a potential of -0.1 V (vs. Ag/AgCl) for glucose detection. Miao *et al.*²⁰¹ constructed a CuO nanoparticle/Nafion modified electrode for H_2O_2 detection. In 0.1 M NaOH, this sensor exhibited a detection limit of 0.06 μM in the range of 0.15 μM –9.00 mM at an applied potential of -0.3 V (vs. SCE). Magnetite has also been reported to own good catalytic activity towards the reduction of H_2O_2 . Lin and Len²⁰⁵ constructed a Fe_3O_4 /chitosan modified glassy carbon rotating disk electrode for a H_2O_2 sensor with unique features of electrocatalytic reduction and interference elimination. This magnetite based H_2O_2 sensor exhibited the advantages of low applied potential (-0.2 V vs. Ag/AgCl), low background current, rapid response and long half-life (9 months at room temperature). Comba *et al.*²⁰⁶ utilized electrosynthesized Fe_3O_4 nanoparticles within a carbon paste electrode to fabricate a glucose sensor. Due to the low operation potential at -0.1 V (vs. Ag/AgCl), this sensor showed no response to 0.1 μM AA and 0.4 μM UA with the average sensitivity of $32 \pm 4 \mu\text{A M}^{-1}$ and detection limit of 3.0×10^{-4} M.

2.5. Other electrocatalytic compounds for hydrogen peroxide sensing

Besides above-mentioned materials, some compounds with reversible redox capabilities have been reported in electrocatalytic H_2O_2 sensing. Metallophthalocyanines and metalloporphyrins such as cobalt phthalocyanine,^{207,208} cobalt tetraruthenated porphyrin,²⁰⁹ ether-linked cobalt phthalocyanine–cobalt tetraphenylporphyrin,²¹⁰ and iron phthalocyanine²¹¹ are frequently used due to their excellent catalytic properties and high chemical stabilities. Perovskite-type oxides containing transition metals,^{212,213} redox polymers,^{162,214} redox dyes²¹⁵ and iron–sulfur protein²¹⁶ have also been proved effective in electrocatalytic H_2O_2 sensing.

3. In vivo applications

When the H_2O_2 sensor is applied to *in vivo* measurements, more challenges will arise. The sensor should be able to provide appropriate spatial and temporal resolution within acceptable sensitivity and limits of detection. Due to the complex environment of *in vivo* measurements, sensing selectivity becomes more critical. Sometimes, a trade-off between selectivity and other parameters such as response time is needed. Furthermore, the sensor should be stable enough to conduct the whole experiment. All of these considerations may be balanced to achieve optimum performance according to the specific requirements and conditions of *in vivo* measurements.

Salazar *et al.*²¹⁷ constructed PB modified carbon fiber microelectrodes for H_2O_2 detection in brain extracellular fluid. To improve stability and selectivity, several polymeric films including Nafion, poly(*o*-phenylenediamine) (PPD), and a hybrid configuration of these two polymers were investigated. The PPD coating was selected due to its excellent anti-interference properties and stabilization capability for PB against solubilisation at high pH though the sensitivity was about 50% loss due to diffusion phenomena across the polymeric film. The result showed that the PPD film significantly enhanced the selectivity against the main endogenous brain interference species, expressed as the ratio of

the sensitivity slopes, which was close to 600 for all interference molecules studied. Later, Salazar *et al.*²¹⁸ adopted the same sensor configuration based on PB for *in vivo* glucose detection in extracellular fluid of the prefrontal cortex. Due to the addition of GOx, Nafion, PEI and PPD were employed to attenuate oxygen dependence, to stabilize the enzyme and to shield the sensor surface from interferences, respectively. The sensor showed the sufficient sensitivity and stability to monitor multi-phasic and reversible changes in brain extracellular fluid.

Kulagina and Michael²¹⁹ reported a cross-linked redox polymer containing a HRP modified carbon fibre electrode which was used for H_2O_2 measurements in the brain of anesthetized rats. When implanted in the striatal region of the rat brain, a biphasic response was observed upon electrical stimulation of the dopaminergic pathway that innervates the striatal tissue, while no response was observed at sensors containing no HRP. This study confirmed that amperometric sensors based on carbon fibre microelectrodes can be used for monitoring the kinetic neurochemical activity in the brain. Rui *et al.*¹¹³ constructed Cyt c adsorbed hexagonal ZnO nanosheets based sensors for the extracellular released H_2O_2 from living cancer cells. The direct electron transfer of Cyt c was realized on the nanostructured ZnO. The result showed that under the optimized potential of 0 V (vs. Ag/AgCl) the electrochemical determination of H_2O_2 is free from both anodic interferences and cathodic interference of O_2 .

A strategy to realize *in vivo* selective detection without sacrifice of response time was reported by Sanford *et al.*²²⁰ The electrochemical technique, background-substrated, fast-scan cyclic voltammetry (FSCV), provides chemical selectivity in addition to high temporal resolution and sensitivity.²²¹ With this approach, a cyclic voltammogram is generated to serve as a chemical signature for the analyte of interest, allowing discrimination from other electroactive species in the brain.¹⁶¹ In this study, the first voltammetric characterization of rapid H_2O_2 fluctuations at an uncoated carbon fibre microelectrode was demonstrated with unprecedented chemical and spatial resolution. The carbon fibre was electrochemically conditioned on the anodic scan and the irreversible oxidation of peroxide was detected on the cathodic scan. The oxidation potential was dependent on the scan rate which occurred at $+1.2$ V (vs. Ag/AgCl) at a scan rate of 400 V s⁻¹. The sensor exhibited a detection limit of 2 μM in a linear range up to 2 mM and was successfully tested in brain slices.

However, *in vivo* biosensors for H_2O_2 were mostly developed for animal tissues. The *in vivo* measurements of H_2O_2 from oxidative bursts in plant (oilseed rape (*Brassica napus* L.)) which were induced by either biotic or abiotic stresses were successfully achieved by our group.^{222–224} The response of the oilseed rape to three different stresses including ultraviolet A and C, *Sclerotinia sclerotiorum* and Cd^{2+} were investigated, respectively. In our studies, a Pt microparticle modified Pt wire electrode with PPD coating as a selectively permeable layer was polarized at -0.1 V (vs. Ag/AgCl) which showed good sensitivity and selectivity in living plant tissues.

4. Conclusions and future prospects

This review has mainly concentrated on the recent advances of electrocatalytic H_2O_2 determination. The utilization of electrocatalytic activity of various materials is for effectively

reducing the overpotentials for H_2O_2 reduction or oxidation, thus decreasing the possible interferences from other electroactive species. Though the earlier studies based on the conventional materials have shown considerable achievements for efficient H_2O_2 determination, the emergence of nanotechnology over the last decade still promoted tremendous progress in this area. Due to their unique physical and chemical properties, nanomaterials not only largely improve the sensitivity and selectivity, but also provide more strategies for H_2O_2 sensing. For example, CNTs and graphene can be used either as substrates with high specific area for catalytic materials or as electrocatalysts by themselves. In addition, nanomaterials facilitate the development of the third generation biosensor in which electrons can be more easily transferred from a protein prosthetic group to an electrode surface. For *in vivo* measurements, besides the above-mentioned merits, nanotechnology is expected to provide very high spatial and temporal resolutions for the analyte of interest with less injury to living organisms since the dimension of the probe can be made small enough in comparison with the size of cell.

On the other hand, research on artificial enzymes that mimic natural enzymes such as CAT is very meaningful. Natural enzymes are difficult to be manipulated for biosensor constructions because they are very sensitive to the environment and prone to denature by relatively harsh conditions such as high temperature or organic solvent. The poor stability of natural enzymes quite limits the fabrication process of biosensors and long-time usage in real applications. Furthermore, the cost of enzymes is still high even in mass manufacturing. In comparison, artificial enzymes can be more robust and more easily tailored to the desired properties for biosensor construction and application. For example, some progress has been made in CAT mimics.^{225–227}

A wide range of newly introduced nanomaterials and electrocatalytic compounds is expected to continuously advance H_2O_2 sensing development. And these sensors will facilitate the understanding of the physiological process participated by H_2O_2 in living organisms. Furthermore, tremendous influence of H_2O_2 sensing on clinical diagnostic, pharmaceutical development, food safety and environmental monitoring will gradually appear in the near future.

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