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Recent strategies to minimise fouling in electrochemical detection systems

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Abstract: Electrode fouling is a phenomenon that can severely affect the analytical characteristics of a technique or a sensor, such as sensitivity, detection limit, reproducibility, and overall reliability. Electrode fouling generally involves the passivation of an electrode surface by a fouling agent that forms an increasingly impermeable layer on the electrode, inhibiting the direct contact of an analyte of interest with the electrode surface for electron transfer. Some potential fouling agents include proteins, phenols, amino acids, neurotransmitters, and other biological molecules. Various antifouling strategies have been reported to reduce or eliminate electrode fouling. Most antifouling strategies exploit a protective layer or barrier on an electrode substrate to prevent the fouling agent from reaching the electrode surface. Although such strategies can be quite effective, they are inappropriate for systems in which the analyte itself is also the fouling agent. In such cases, other strategies must be used, including electrode surface modification and electrochemical activation. In this review, recent strategies to minimise and efforts to overcome electrode fouling across a diverse range of analytes and fouling agents will be presented.

Keywords: chemical fouling; fouling during neurotransmitter detection; strategies for minimising electrode fouling.

Introduction

Fouling of an electrode surface is often a serious problem encountered in some electrochemical analyses. This phenomenon may negatively affect the analytical characteristics of a technique or a sensor, such as sensitivity, detection limit, reproducibility, and overall reliability (Godino et al. 2010, Gao et al. 2011, Gasnier et al. 2012, Teymourian et al. 2012, Roeser et al. 2013, Sharp 2013, Brocenschi et al. 2014, Cavanillas et al. 2014, Chira et al. 2014, Schmidt et al. 2014, Stoytcheva et al. 2014). Electrode fouling can thus significantly affect the performance and reliability of electrochemical techniques and sensors in many applications.

Electrode fouling is a broad term generally describing the passivation of an electrode surface by a fouling agent that forms an increasingly impermeable layer on the electrode (Gattrell and Kirk 1992, Gao et al. 2011, Casella and Contursi 2012, Gasnier et al. 2012). This occurs by a wide range of mechanisms predominantly depending on the identity of the responsible fouling agent. The fouling agent may be a component of the matrix, the analyte itself, or a product of the electrochemical reaction. Electrode fouling prevents an analyte of interest from making physical contact with the electrode for electron transfer to elicit an electrochemical response (Narmadha et al. 2011, Mudrinić et al. 2014, Muna et al. 2014, Stoytcheva et al. 2014). The fouling agent may specifically adhere to certain structural features present on the electrode surface, such as edges and grain boundaries (Wilson et al. 2005, Goto et al. 2011, Zhuiykov and Kalantar-zadeh 2012). The fouling agent tends to adhere to the electrode surface as a result of favourable interactions between the fouling agent and the electrode surface. This includes hydrophobic, hydrophilic, and electrostatic interactions depending on the particular chemistries of the fouling agent and the electrode surface.

Electrodes that tend to have hydrophobic surfaces, such as diamond, carbon nanotubes, and some other carbon-based electrodes (Shin et al. 2005, McCreery 2008, Goto et al. 2011, Roeser et al. 2013), can promote species possessing hydrophobic components, including aromatic compounds, saturated or aliphatic compounds, and proteins to adhere to and foul the electrode. The hydrophobic interactions are entropically favourable in an aqueous electrolyte because water molecules are released from the solvation shell around hydrophobic compounds or components (Malmsten 2003, Wilson et al. 2005). These interactions are sufficiently favourable such that fouling

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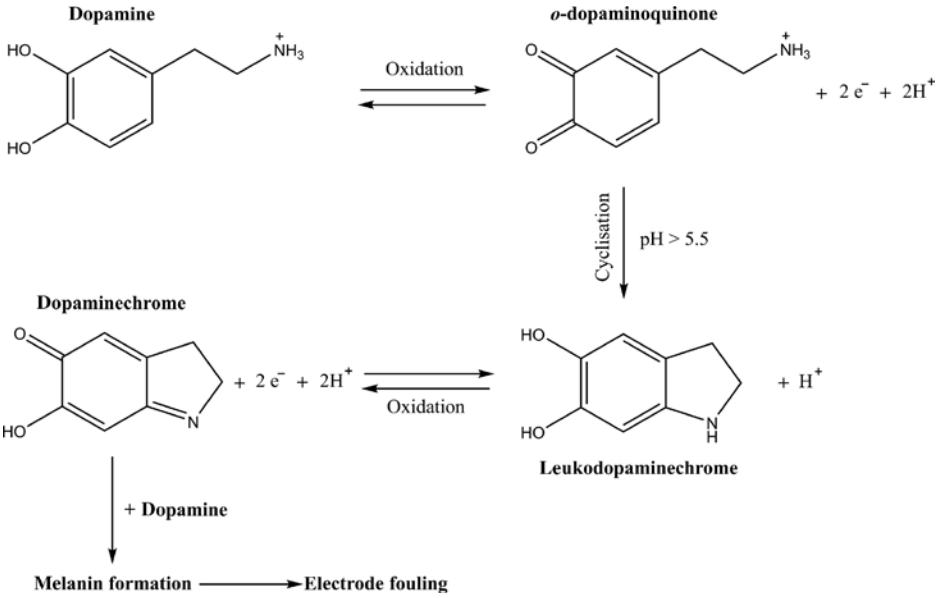
by a hydrophobic mechanism is typically irreversible in an aqueous electrolyte under mild conditions (Grinnell and Feld 1981, Malmsten 2003).

Fouling that occurs by hydrophilic interactions tends to be more reversible than fouling involving hydrophobic interactions (Grinnell and Feld 1981, Hess and Vogel 2001, Malmsten 2003, Wilson et al. 2005, Thevenot et al. 2008). This greater reversibility in aqueous electrolytes containing a strong polar solvent, for example, water, is because the hydrophilic and electrostatic interactions are not exclusive to the fouling agent and the electrode surface, as water also has compatible hydrophilic (dipole-dipole interactions or hydrogen bonding) and electrostatic properties (ion-dipole interactions). In the case of electrostatic interactions, the electrode surface may possess ionisable functional groups, such as carboxylic acids, which will bind with a suitable fouling agent (Shin et al. 2005, McCreery 2008). Electrode fouling that occurs by a hydrophilic or electrostatic interaction is associated with polar, hydrophilic, or charged species, including proteins and other biological molecules.

Electrode fouling that occurs by the adsorption of biological macromolecules is frequently due to proteins as a result of their abundance in biological samples and tendency to cause fouling. The adsorption of other biological materials, such as cells, cell fragments, and DNA/RNA, can also foul an electrode. The binding of cells to an electrode surface is often mediated by proteins (Wilson et al. 2005). Soluble proteins are interesting fouling agents, as they are often hydrophilic on the surface to interact with an aqueous environment as well as hydrophobic on the inside to maintain protein folding or the binding of hydrophobic materials (Malmsten 2003). As a result of the dual nature of most proteins, they can foul electrodes through both hydrophilic and hydrophobic interactions. To foul a hydrophobic electrode surface, many proteins will unfold to allow the hydrophobic residues to interact with the hydrophobic surface (Grinnell and Feld 1981, Malmsten 2003, Wilson et al. 2005, Thevenot et al. 2008). Due to the greater strength of hydrophobic interactions in aqueous systems (Grinnell and Feld 1981, Hess and Vogel 2001, Malmsten 2003, Wilson et al. 2005, Thevenot et al. 2008), many antifouling strategies aimed at reducing fouling by biological materials involve increasing the hydrophilicity of the electrode surface.

Fouling agents discussed thus far have been monomeric species, where it is more energetically favourable for the fouling agent to adsorb to the electrode surface rather than be in solution. A fouling agent may also be a polymeric species that forms in the electrolyte, usually as a result of an electrochemical reaction (Gattrell and Kirk 1992, 1993, Anandhakumar et al. 2010, Narmadha et al. 2011, Pirvu and Manole 2013, Yang et al. 2013, Muna et al. 2014, Quynh et al. 2014). The product of an electrochemical reaction may be reactive, such that it forms dimers or larger polymeric structures. These polymeric structures are often insoluble due to their large size and high molecular weight and will precipitate from solution on the nearest surface, such as the electrode surface. Such adhesion of a polymer to the electrode surface obstructs the ability of the analyte to reach the electrode surface, thereby fouling the electrode (Gattrell and Kirk 1992, Anandhakumar et al. 2010, Narmadha et al. 2011, Pirvu and Manole 2013, Yang et al. 2013, Quynh et al. 2014). The polymer may be a dense and closed structure that is impermeable, or it may be lighter and more open such that the polymer is permeable or semipermeable (Paul et al. 2013, Pirvu and Manole 2013, Yang et al. 2013). The permeability of the polymeric species will depend on the starting monomer and the electrochemical system conditions (Anandhakumar et al. 2010, Narmadha et al. 2011). The important analytes of interest that foul electrodes by this route are phenols and neurotransmitters. In the case of phenols, following anodic oxidation, radicals are formed. Further reactions involving the radicals may produce soluble species, such as hydroquinone/benzoquinone or catechol, or may undergo coupling reactions to form dimers, then oligomers, and finally polymers (Gattrell and Kirk 1992, 1993). During the detection of the neurotransmitter, dopamine, the reaction products, including leukodopaminechrome (LDC) and dopaminechrome (DC), can lead to the formation of melanin-like polymeric molecules of ~3.8 Å in size that foul the electrode (Lee et al. 2007, Harreither et al. 2013, Trouillon et al. 2014). Specifically, dopamine is electrochemically oxidised to *o*-dopaminoquinone that is subsequently cyclised leading to the formation of LDC. In the following step, LDC is further oxidised to yield DC that may polymerise into a melanin-like molecule, as depicted by the mechanism shown in Scheme 1. These molecules can form strong covalent bonds with organic moieties and noncovalent bonds with inorganic groups present on an electrode surface (Lee et al. 2007, Harreither et al. 2013, Trouillon et al. 2014).

The types of fouling agents and the ways in which they cause electrode fouling are exceedingly broad. Equally broad are the strategies that have been used to reduce electrode fouling or impart some fouling resistance to an electrochemical technique or sensor. Most antifouling strategies use a modified electrode that has greater fouling resistance than an unmodified electrode. With the tendency



Scheme 1: A mechanism proposed by Harreither et al. (2013) for electrode fouling during the electrochemical oxidation of dopamine in aqueous solutions.

of glassy carbon, graphite, and metallic electrodes to be heavily fouled by a large variety of fouling agents, these electrode materials are commonly modified to increase fouling resistance (Gao et al. 2011, Gasnier et al. 2012, Teymourian et al. 2012, Roeser et al. 2013, Chira et al. 2014). Carbon-based materials, such as carbon nanotubes or graphene, have been used as electrode coatings due to their large surface area, electrocatalytic properties, and fouling resistance (Shan et al. 2009, Zhou et al. 2009, Gasnier et al. 2012, Teymourian et al. 2012). Metallic nanoparticles also possess important electrocatalytic properties and high electrical conductivity and can exhibit antifouling properties (Safavi and Momeni 2010, Muna et al. 2014). Polymers including Nafion (Razmi and Heidari 2009, Trouillon et al. 2009, Singh et al. 2011), poly(ethylene glycol) (Liu et al. 2011, Picher et al. 2013), poly(vinyl chloride) (Kivlehan et al. 2012), poly(3,4-ethylenedioxythiophene) (PEDOT; Yang et al. 2013), and polypyrrole (Pirvu and Manole 2013, Sasso et al. 2013) may be used as a coating to prevent the fouling agent from reaching the electrode surface. Although proteins are often fouling agents, they have been immobilised on electrode surfaces to prevent the nonspecific adsorption of other proteins or fouling agents (Picher et al. 2013, Qiu et al. 2013). Another potential benefit of this antifouling strategy is that enzymes can be immobilised to catalyse a reaction as part of the detection process, such as horseradish peroxidase and the detection of 4-chlorophenol (Qiu et al. 2013). Enzyme immobilisation can thus reduce both enzyme loss and the adsorption of potential fouling agents.

Electrochemical analyses are increasingly utilising uncoated electrodes with antifouling properties, especially boron-doped diamond electrodes. While pure diamond has a very low electrical conductivity due to a completely sp^3 structure, doping with boron sufficiently increases the conductivity for use as an electrode material (McCreery 2008). The extensive sp^3 structure of boron-doped diamond together with the typically low surface polar functional groups results in a dramatic decrease in the adsorption of certain fouling agents (Shin et al. 2005, McCreery 2008). Nanoporous gold electrodes are another type of uncoated electrode with strong antifouling properties as a result of their increased electrode porosity and surface area compared to the frequently fouled planar gold electrodes (Summerlot et al. 2011, Patel et al. 2013b, Tavakkoli and Nasrollahi 2013, Quynh et al. 2014).

Although many antifouling strategies rely on the electrode material or coating to alleviate fouling, there are also other strategies for minimising electrode fouling during analyses using conventional electrodes. In electrochemical activation, a single potential or a train of pulses is applied to modify the electrode surface chemistry or remove adsorbed material through physical or oxidative processes (Dejmkova et al. 2009, da Silva et al. 2013). Surfactants or organic solvents can be included in the electrolyte to increase the solubility of reaction products that may adsorb on the electrode surface (Anandhakumar et al. 2010, Narmadha et al. 2011). The surfactants may also adsorb on the electrode surface, providing a physical barrier between the surface and potential fouling agents

(Malmsten 2003, Anandhakumar et al. 2010). Analogous to the process of electrode fouling, the choice and success of any antifouling strategy will depend on the particular analyte, potential fouling agents, matrix, and conditions used.

In this review, we have described the selected progresses in reducing electrode fouling published over the period from 2009 to early 2015. Due to the diversity of fouling agents and antifouling strategies investigated in this period, the evaluation or comparison of one strategy over another for a particular application is not straightforward. This review is not intended to be a comprehensive review covering all developments in this period, but instead we have sought to provide an overview and discussion of recent significant strategies for reducing fouling. No previous review is known to focus on the multiple aspects of electrode fouling and discuss diverse antifouling strategies in the one article. This review has been organised by categorising antifouling strategies into three main sections: electrode coatings and modifications, electrochemical activation, and electrolyte and flow systems. In each section, we have provided as many relevant examples as possible to illustrate the feasibility and effectiveness of the developed strategies for electrode fouling prevention or reduction. Examples involving more than one antifouling strategy were placed in the section for the most important or effective strategy.

Electrode coatings and modifications

Carbon-based materials

Carbon nanotubes

Carbon nanotubes are commonly immobilised on electrode surfaces due to their large surface area, electrical conductivity, and electrocatalytic properties (Gasnier et al. 2012, Teymourian et al. 2012). Carbon nanotube-modified electrodes also exhibit antifouling properties. For example, a multiwalled carbon nanotube-modified glassy carbon electrode was successfully used in the analysis of Sudan I, which is a phenolic azo dye (Yang et al. 2010). This modified electrode significantly reduced fouling due to the polymeric products of Sudan I compared to a bare glassy carbon electrode. In an amperometric analysis, the modified electrode lost only 15% of the initial current after 90 min compared to the bare glassy carbon electrode in which the current decreased more than 50% in <20 min. In addition to the greater fouling resistance of the carbon nanotube-modified electrode, the high surface area of the carbon nanotubes increased the measured current (Yang et al. 2010). Carbon nanotubes have also shown antifouling properties in an electrochemical analysis *in vivo*, where proteins of all sizes could potentially foul the electrode surface. For an *in vivo* analysis, Xiang et al. (2014) immobilised vertically aligned carbon nanotubes on SiO_2 passivated carbon fibres. This electrode was prepared by the pyrolysis of iron phthalocyanine under an Ar/H_2 atmosphere at 800°C to 1100°C. In applying the electrode to selectively monitor 0.5 mᴍ ascorbate in cerebrospinal fluid *in vivo*, the authors reported a 2% loss of sensitivity in a 30-min experiment. In contrast, a corresponding 21% loss was observed at a bare carbon fibre microelectrode. The modified electrode was also used to successively detect ascorbate in the striatum of anesthetised rat brain every 5 min (Xiang et al. 2014). Excellent reproducibility and durability, along with well-defined sigmoidal voltammograms of ascorbate in the rat brain, supported an antifouling capability of the carbon nanotube-modified electrode in a complex sample. The antifouling properties of carbon nanotubes may be due to their electrocatalytic activity that arises from various defects at the ends of the nanotubes or on the cylindrical walls (McCreery 2008, Gasnier et al. 2012, Teymourian et al. 2012). These defects often undergo oxidation or other reactions producing a variety of functional groups.

Although the carbon nanotube-modified electrodes prepared by Yang et al. (2010) and Xiang et al. (2014) used a suspension of the nanotubes in *N*,*N*-dimethylformamide and pyrolysis of iron phthalocyanine, respectively, a polymer is frequently used to reduce the aggregation of the nanotubes (Gasnier et al. 2012, Teymourian et al. 2012). For the analysis of phenolic flavones, Sheng et al. (2014) and Chen et al. (2011b) prepared multiwalled carbon nanotube composite electrodes using two different polymers. In the analysis of 5,7-dihydroxychromone and luteolin, an electrode with the polymer poly(ethylene terephthalate) was used in conjunction with capillary electrophoresis (Sheng et al. 2014). It was found that the current at this electrode diminished by 7.1% [relative SD (RSD) 2.6%] after 15 repetitive runs. The electrode prepared by Chen et al. (2011b) showed a very similar performance in the analysis of various phenolic flavones. The electrode was prepared by the water vapour-initiated polymerisation of ethyl 2-cyanoacrylate with multiwalled carbon nanotubes. Coupled with capillary electrophoresis, the current at this electrode decreased by up to 7.8% after 15 runs (RSD 2.7%). In both studies, the antifouling properties of carbon nanotubes were illustrated with an analogous composite electrode where the carbon nanotubes were replaced with graphite. These graphite composite electrodes experienced 42% to 43% (RSD 18–19%) decrease in current. These results suggest that the observed fouling resistance is due to the carbon nanotubes and the particular polymer used to construct the electrode has little impact on the fouling resistance. The electrodes used by Sheng et al. (2014) and Chen et al. (2011b) were constructed without a solid electrode substrate by placing the carbon nanotube-polymer mixtures inside fused silica capillaries. This avoids issues with possible detachment of the carbon nanotube-polymer layer from an electrode surface.

Although carbon nanotubes have been shown to be resistant to fouling from phenolic analytes that polymerise during electrochemical detection, such as Sudan I (Yang et al. 2010) and phenolic flavones (Chen et al. 2011b, Sheng et al. 2014), they are also resistant to polyphenols present in white wine. Although these polyphenols are not a product of the electrochemical process, they can nevertheless adsorb on the electrode surface. To analyse the polyphenols present in white wine, Moreno et al. (2011) used multiwalled carbon nanotubes dispersed in the polymer polyethylenimine on a glassy carbon substrate. With the use of capillary zone electrophoresis, no decrease in current was observed after eight runs. The presence of the carbon nanotubes significantly improved the fouling resistance of the electrode, as the current at a bare glassy carbon electrode decreased by 82% after eight runs.

In addition to polymers, other materials have been used to increase carbon nanotube dispersion to improve electrode performance. Gasnier et al. (2012) observed that the presence of the neurotransmitter, dopamine, could improve the dispersion and mechanical strength of carbon nanotubes when applied to an electrode surface. This electrode was prepared by immobilising multiwalled carbon nanotubes dispersed in a solution of polyethylenimine functionalised with dopamine on a glassy carbon electrode (Gasnier et al. 2012). The addition of dopamine also resulted in a lower oxidation potential of nicotinamide adenine dinucleotide (NADH; Gasnier et al. 2012). Using the modified electrode, a series of 10 amperometric calibrations was performed. Between the 1st and 10th calibrations, the sensitivity to NADH decreased by only 12% (Gasnier et al. 2012). These results demonstrate the resistance of the modified glassy carbon electrode to fouling by NAD^+. Although dopamine has a tendency to cause electrode fouling, its use significantly improved the dispersion of the carbon nanotubes in solution through hydrophobic interactions and thus may have contributed to the good antifouling properties. Zestos et al. (2014) also developed a modified electrode using polyethylenimine and carbon nanotubes. A carbon nanotube fibre electrode was prepared by suspending single-walled carbon nanotubes in water with sodium dodecylbenzenesulfonic acid and pumping the suspension into a rotating solution of polyethylenimine in a custom-built rotating stage. The fouling resistance of the polyethylenimine-carbon nanotube fibre electrodes was examined by measuring serotonin in the presence of the metabolite of serotonin, 5-hydroxyindolacetic acid, which is also known to cause electrode fouling during the detection of serotonin *in vivo*. Electrode fouling from the metabolite of serotonin is particularly important because its physiological concentration is often 10 times higher than that of serotonin. The serotonin oxidation peak at the polyethylenimine-carbon nanotube electrode was reported to remain almost constant upon incubation in 5-hydroxyindolacetic acid for 2 h. The polyethylenimine-carbon nanotube fibre electrodes have also exhibited antifouling properties towards the oxidation product of dopamine, as no significant change in dopamine oxidation current was observed when a bolus of dopamine was injected every 2 h over a 10-h period (Zestos et al. 2014). When the polyethylenimine-carbon nanotube fibre electrodes were applied to measure exogenous serotonin in rat brain slices of the caudate putamen for 10 min, the peak-shaped cyclic voltammograms and the dopamine oxidation peak current remained unchanged. The authors proposed that the antifouling properties of the electrode are due to the presence of additional edge plane sites arising from carbon nanotubes. Similarly, Harreither et al. (2013) developed a 35 μm diameter carbon nanotube fibre by continuously spinning single-walled carbon nanotubes dispersed in sodium dodecyl sulfate in a coflowing stream of aqueous poly(vinyl alcohol). Based on a steady-state amperometric measurement of 1 mᴍ and 100 μᴍ dopamine at the fabricated electrode, as shown in Figure 1, they found that the electrode lost half of its initial steady-state current in 15 min at the high concentration (Harreither et al. 2013). However, the steady-state current obtained in 100 μᴍ dopamine was unchanged for 2 h. The experiment may be a good indication of the potential application of carbon nanotube fibres in the brain, where the concentration of dopamine (0.01–1 μᴍ) is much lower than that used in this experiment. These results also indicated that fouling of dopamine is concentration dependent and a lower concentration of dopamine may lead to decreased chemical fouling. The authors also explained that the insulating patches grew at a slower rate on carbon nanotube fibre compared to traditional carbon fibre.

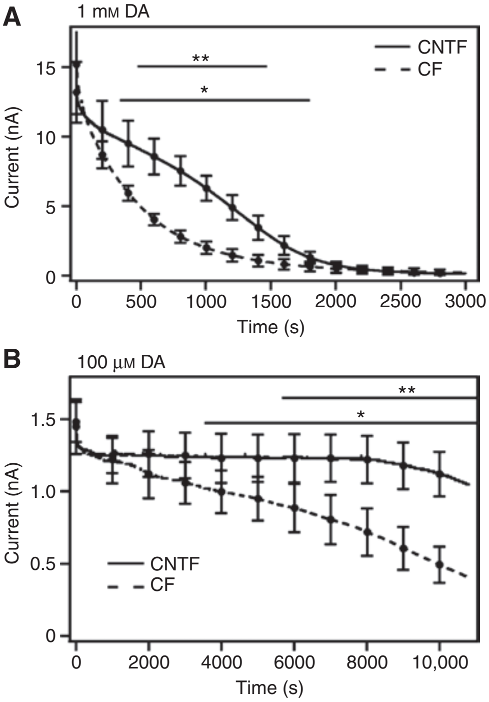


Figure 1: Amperometric currents for 1 mM dopamine (A) and 100 μM dopamine (B) obtained at 0.8 V versus Ag|AgCl with a carbon nanotube fibre microelectrode (solid line) and a carbon fibre microelectrode (dashed line) in phosphate-buffered saline (pH 7.4).
Mean±SD (n=4–7). The results were compared using Student's t-test, *p<0.05, **p<0.01. Reproduced with permission from Harreither et al. (2013).

Without the use of a polymer, Zheng et al. (2012) constructed a glassy carbon electrode modified with multiwalled carbon nanotubes dispersed in a gel containing the ionic liquid, 1-butyl-3-methyl-imidazolium hexafluorophosphate. This ionic liquid-modified electrode was used for the analysis of *o*-sec-butylphenol and displayed moderate antifouling properties. The current density was observed to have decreased by 25% in the second cycle relative to the first cycle. Despite being a large decrease in current density, a 51% and 49% decrease in current density was measured at a bare glassy carbon electrode and a multiwalled carbon nanotube-modified glassy carbon electrode, respectively. In this study, the carbon nanotube-modified electrode without the ionic liquid showed virtually identical fouling resistance to a bare glassy carbon electrode. This is in contrast to the study of Yang et al. (2010), where a similarly prepared carbon nanotube electrode was found to have good antifouling properties towards Sudan I. The observed difference in fouling resistance appears to be due to the properties of the particular analytes involved.

As the walls of carbon nanotubes are generally hydrophobic with strong π-π interactions between their aromatic rings (Gasnier et al. 2012), fouling resistance to some aromatic fouling agents may be improved by increasing the hydrophilicity of the carbon nanotubes. Merli et al. (2012) and Thomas et al. (2013) both prepared electrodes with oxidised carbon nanotubes that resisted fouling agents possessing aromatic functional groups. Olanzapine and risperidone are two pharmaceutical drugs that can form oligomers during electrochemical analysis (Merli et al. 2012). Merli et al. (2012) developed an oxidised single-walled carbon nanotube-modified gold electrode for the analysis of these drugs. They found that, after more than 20 differential pulse voltammetric scans, there was no apparent fouling of the modified electrode for both drugs. Similarly, for the analysis of the amino acid tryptophan, Thomas et al. (2013) constructed an oxidised multiwalled carbon nanotube-modified carbon paste electrode that demonstrated good antifouling properties, with a negligible change in current after 30-min continuous amperometry. The oxidation of the carbon nanotubes would have increased the hydrophilicity with a greater number of surface oxygen functional groups, which may have reduced the adsorption of these aromatic species on the carbon nanotubes.

Graphene

Graphene is a two-dimensional single layer of sp^2 carbon atoms with very high electrical conductivity, surface area, and mechanical strength (Shan et al. 2009, Zhou et al. 2009). It can be considered as an individual layer of graphite or an unrolled carbon nanotube and has been shown to reduce electrode fouling. The most common method to prepare graphene is by oxidising graphite and separating into single layers to form graphene oxide, which is then chemically or electrochemically transformed to reduced graphene oxide. For example, Alwarappan et al. (2010) studied the direct electrochemical activity of cytochrome *c* at a chemically reduced graphene-modified glassy carbon electrode. In addition to improved electron transfer kinetics, the current at the modified electrode decreased by only 7.5±0.3% after 50 repetitive cycles (Alwarappan et al. 2010). The presence of graphene protected the electrode from fouling by preventing cytochrome *c* from reaching the glassy carbon electrode surface and provided electrocatalytic sites for the efficient detection of the protein. Similar to carbon nanotubes, electrocatalytic sites may be made up of the various surface oxygen functional groups and defects on the graphene. Although reduced graphene is obtained in the graphene oxide route, not all oxygen functionalities are removed and defects in the carbon lattice may still be present. Graphene that is more hydrophobic with fewer oxygen functionalities could be advantageous for minimising fouling from certain species. Keeley et al. (2011) prepared such low-oxygenated graphene by the *N*,*N*-dimethylformamide exfoliation of graphite powder. After 60-min continuous amperometry, a glassy carbon electrode modified with this exfoliated graphene showed only a 15% decrease in the oxidation current of NADH, whereas an analogous graphene oxide-modified electrode showed a corresponding 63% decrease. These results support the suggestion that the absence of oxygen functionalities in this exfoliated graphene significantly reduce the adsorption of NAD^+, minimising electrode fouling (Keeley et al. 2011).

Similar to carbon nanotubes, graphene can be combined with polymers and other materials to improve the stability and performance of a graphene-modified electrode. Chen et al. (2011a) developed a graphene/poly(urea-formaldehyde) composite platinum electrode for the determination of salidroside and tyrosol phenols. After 15 measurements, the current decreased by 8.1% and 43.9% at the composite electrode and bare platinum electrode, respectively. The polymer used in this graphene composite electrode assisted in binding the carbon material to the electrode surface and ensuring the surface was completely protected from fouling agents. In place of a polymer, Raj and John (2014) pretreated a glassy carbon electrode with 1,6-hexadiamine before adding graphene oxide to the treated surface and then electrochemically reducing the graphene oxide. This modified electrode was shown to be resistant to fouling by the oxidation products of theophylline, a methylxanthine derivative used as a pharmaceutical drug. In their work, there was a negligible change in current (RSD 0.85±0.04%) at the graphene-modified glassy carbon electrode after 25 cycles, indicating minimal fouling by the oxidation of theophylline (Raj and John 2014). The modified electrode showed higher fouling resistance than the corresponding bare glassy carbon and graphene oxide-modified glassy carbon electrodes. The lower fouling resistance of the graphene oxide-modified electrode is probably due to the many hydrophilic functional groups, which would increase the adsorption of the polar theophylline molecule and oxidation products. Similar to poly(urea-formaldehyde), 1,6-hexadiamine has enhanced the adsorption of reduced graphene oxide to the surface, which formed a barrier between the underlying electrode surface and the theophylline oxidation products.

Diamond and other carbon-based materials

Diamond has a very low electrical conductivity due to a completely sp^3 structure, but doping with boron sufficiently increases the conductivity for use as an electrode material (McCreery 2008). The extensive sp^3 structure of boron-doped diamond, together with the typically low surface polar functional groups, results in a dramatic decrease in the adsorption of certain fouling agents (Shin et al. 2005, McCreery 2008). The surface chemistry and shape of an electrode can, however, have a major effect on the electrochemical performance and antifouling characteristics. Indeed, Trouillon et al. (2011) demonstrated that the boron doping level affects the antifouling properties of boron-doped diamond electrodes. They investigated a range of boron doping levels (0.1, 1, and 5%, v/v) to investigate the stability of the electrodes for the detection of dopamine with bovine serum albumin as a biological fouling agent. Albumin is commonly used to test the antifouling properties of electrodes and sensors because it is often considered a biological fouling standard (Grinnell and Feld 1981, Wilson et al. 2005, Thevenot et al. 2008, Trouillon et al. 2009). A nonsignificant decrease of dopamine oxidation current was observed at the 0.1% and 1% doping levels. However, a corresponding 25% decrease was observed when the doping level was increased to 5%. These results indicate that high-density boron-doped diamond electrodes are more prone to fouling. A high level of boron doping would facilitate the formation of a high density of defect sites that are electrocatalytically active. Consequently, the inactivation of these defect sites by fouling agents would result in diminished electrochemical detection of the analyte. Therefore, low-level boron-doped diamond electrodes should limit the adsorption of fouling agents on an electrode surface. For example, Zhao et al. (2010) fabricated a conical-tip boron-doped diamond microelectrode with a low doping level. No significant attenuation in the oxidation signal was observed during the amperometric detection of serotonin in guinea pig mucosa *in vitro* for 100 min. As well as the doping level, the surface termination and roughness affect the fouling resistance of boron-doped diamond electrodes. Shpilevaya and Foord (2014) examined the extent of fouling by methyl viologen dichloride hydrate and 9,10-anthraquinone-2,6-disulfonic acid disodium salt and their products on various diamond electrodes, including microcrystalline boron-doped diamond, boron-doped diamond powder, and detonation nanodiamond powder. The effect of electrode fouling was also investigated at H- and O-terminated electrodes, which have low and high proportions of surface oxygen functionalities, respectively. There was no observable adsorption of both compounds or products at O-terminated diamond electrodes (Shpilevaya and Foord 2014). On the contrary, there was a significant adsorption at the H-terminated electrodes. For methyl viologen, although the microcrystalline boron-doped diamond electrode showed the highest quantity of adsorbed product at 10.8 nmol cm^{-2}, it was the boron-doped diamond powder and detonation nanodiamond powder electrodes that exhibited a greater tendency to permanently adsorb the methyl viologen product (Shpilevaya and Foord 2014). After rinsing all three electrodes with water, the quantity of remaining adsorbed product was 0.4 and 1.2 nmol cm^{-2} for the boron-doped diamond powder and detonation nanodiamond powder electrodes, respectively, compared to only 0.1 nmol cm^{-2} for the microcrystalline boron-doped diamond electrode. For anthraquinonedisulfonate, however, the detonation nanodiamond powder electrode showed the highest quantity of adsorbed material at 18 and 15 nmol cm^{-2} for the reduction and oxidation scans, respectively, whereas the boron-doped diamond powder and detonation nanodiamond powder electrodes again showed a greater tendency to permanently adsorb material (Shpilevaya and Foord 2014). From the results, it is apparent that the hydrophobicity of the H-termination increases the extent of electrode fouling for these analytes as well as the greater surface roughness of the diamond powder electrodes compared to the microcrystalline boron-doped diamond (Shpilevaya and Foord 2014). For the analysis of serotonin, Güell et al. (2010) also observed that O-terminated boron-doped diamond electrodes had superior antifouling properties compared to a carbon nanotube network electrode after 10 consecutive scans.

In comparing the fouling resistance of boron-doped diamond (sp^3-hybridised carbon), undoped graphene (sp^2-hybridised carbon), and boron-doped graphene (sp^2-hybridised carbon) electrodes, Tan et al. (2013) found that, after 20 consecutive cyclic voltammetric scans in NADH, the boron-doped diamond electrode had a greater fouling resistance than both graphene-modified electrodes. These results support that the more inert sp^3 surface of diamond has lower surface oxygen functionalities and higher hydrophobicity than graphene. Similarly, Patel et al. (2013a) compared a boron-doped diamond electrode to several other carbon-based electrodes in the analysis of dopamine. The O-terminated polycrystalline boron-doped diamond electrode was considered the least susceptible to fouling even in a high concentration of 1 mM dopamine compared to glassy carbon, edge plane pyrolytic graphite, basal plane pyrolytic graphite, and basal plane highly oriented pyrolytic graphite, as depicted in Figure 2.

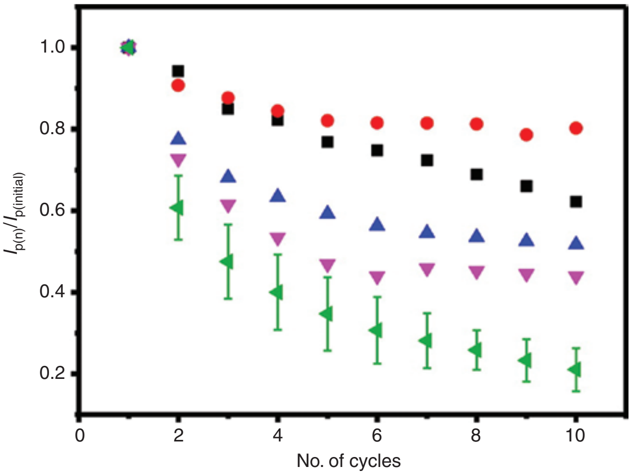


Figure 2: $I_{p(n)}/I_{p(initial)}$ against number of cycles (*n*) for the electrooxidation of dopamine at polycrystalline boron-doped diamond (red), glassy carbon (black), edge plane pyrolytic graphite (blue), basal plane pyrolytic graphite (pink), and basal plane highly oriented pyrolytic graphite (green).
The five grades of basal plane highly oriented pyrolytic graphite are plotted as mean±SD. Reproduced with permission from Patel et al. (2013a).

Similar to boron-doped diamond electrodes, diamond-like carbon electrodes are amorphous carbon with a high proportion of diamond-like bonds (sp^3), which provides good resistance to electrode fouling (Goto et al. 2011). The fouling resistance of a diamond-like carbon electrode treated with oxygen plasma to increase hydrophilicity has been investigated using bovine serum albumin, DNA, and human serum (Goto et al. 2011). There was a negligible change in the current response to ferricyanide/ferrocyanide after incubation in solutions of bovine serum albumin, DNA, and human serum for up to 24 h. The very strong resistance to fouling at the electrode is likely the result of the generally inert sp^3 diamond-like structure that reduces adsorption. Similar to Shpilevaya and Foord (2014) and Tan et al. (2013), where hydrophilicity was considered to be important for fouling resistance, increasing the surface hydrophilicity of the diamond-like carbon electrode with oxygen plasma treatment has likely improved the fouling resistance to these biological fouling agents and matrices. This would minimise the tendency of proteins to unfold and foul by hydrophobic mechanisms, which is considered to be stronger than hydrophilic adsorption (Grinnell and Feld 1981, Hess and Vogel 2001, Malmsten 2003, Wilson et al. 2005, Thevenot et al. 2008). On the contrary, Chandra et al. (2014) reported physically small conical-tip carbon electrodes (~2–5 μm diameter and ~4 μm axial length) that were hydrogenated by plasma-enhanced chemical vapour deposition to achieve an H-terminated diamond-like sp^3 electrode surface. These electrodes retained 65% of dopamine oxidation current after they were incubated in a laboratory synthetic fouling solution containing caproic acid (a lipid), bovine serum albumin (a protein), cytochrome *c* (a protein), and human fibrinopeptide B (a peptide) for 7 days. By implanting the electrode in the left striatum of a male Sprague-Dawley rat during 60-min *in vivo* experiments, more than 70% of the dopamine oxidation current remained after the first 30 min and 50% remained over the next half period of the experiment, as shown in Figure 3. Although these results can be attributed to the H-terminated hydrophobic surface, the hydrophilic oxygen plasma-treated diamond-like electrode appeared to have a greater resistance to fouling.

An electron cyclotron resonance-sputtered nanocarbon film is a carbon electrode with similar properties to diamond-like carbon electrodes and has both sp^2 and sp^3 characteristics (Kato et al. 2011, Xue et al. 2012). Kato et al. (2011) and Xue et al. (2012) both prepared oxidised electron cyclotron resonance-sputtered nanocarbon films to resist fouling by bovine serum albumin and 8-hydroxy-2′-deoxyguanosine, respectively. The electrode used by Kato et al. (2011) was anodically pretreated to oxidise the electrode surface. Coupled with flow injection analysis, there was a negligible decrease in the current at this electrode after 12 injections (RSD 0.75%). At a bare glassy carbon electrode, the current was highly variable, fluctuating over the 12 injections (RSD 9.28%). The authors suggested that the greater fouling resistance of the pretreated nanocarbon film electrode was due to the increased hydrophilicity from oxidation. To oxidise their nanocarbon film, Xue et al. (2012) treated the electrode with oxygen plasma to partially oxidise the electrode surface. After a 30-min incubation in bovine serum albumin, the peak separation of ferricyanide/ferrocyanide increased from 80 to 120 mV and the peak current decreased to 92.0% of the initial value. On the contrary, for a pristine electron cyclotron resonance-sputtered nanocarbon film electrode without the oxygen plasma treatment, the peak separation increased from 217 to 620 mV and the peak current decreased to 71.7% of the initial value, which illustrated the requirement of a partially oxidised surface for antifouling properties. Compared to glassy carbon electrodes, the treated nanocarbon film electrode also demonstrated superior fouling resistance and was slightly improved compared to diamond-like carbon electrodes. The nanocarbon film electrode treated with oxygen plasma remained relatively hydrophobic compared to glassy carbon electrodes and diamond-like carbon electrodes, which suggests that, in addition to hydrophilicity, there are other important factors influencing the antifouling properties (Xue et al. 2012). For example, surface flatness is also believed to contribute to the observed fouling resistance, as the nanocarbon films were much smoother than diamond-like carbon electrodes (Kato et al. 2011, Xue et al. 2012).

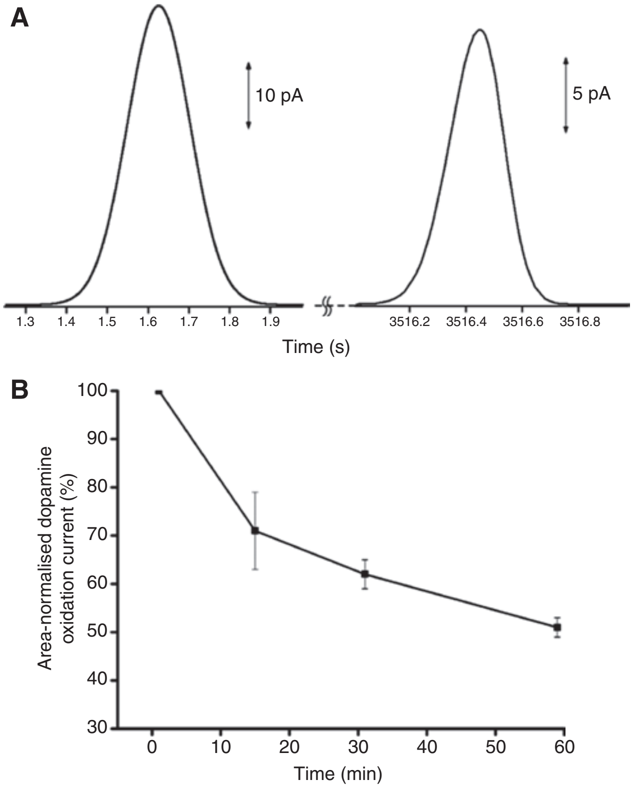


Figure 3: Gaussian-fitted dopamine oxidation signals obtained upon repeated electrical stimulations in the rat striatum at the start (left) and after 60 min (right) of monitoring at a hydrogenated carbon electrode (A) and a plot of electrode area normalised current measured over a 60-min period at hydrogenated carbon electrodes implanted in the rat striatum (B).
Reproduced with permission from Chandra et al. (2014).

Although sp^2-hybridised carbon materials, such as graphite and glassy carbon, are often found to significantly foul with a variety of species, some sp^2 carbon materials have shown strong antifouling properties, such as the NADH sensor developed by Gao et al. (2011) using a carbon double-shelled hollow sphere-modified glassy carbon electrode. The current at this modified electrode decreased by 16.0% after 4000 s, whereas the current at a bare glassy carbon electrode decreased by 52.6% (Gao et al. 2011). The antifouling and electrocatalytic properties of the carbon hollow spheres were suspected to be due to the presence of a glassy carbon surface with surface oxygen functionalities and defects. Although such surface features have been considered to contribute to increased fouling with other species, the spherical shape and small size of the carbon hollow spheres may have resisted the adsorption of NAD$^+$. Similarly, Hadi and Rouhollahi (2011) analysed the thiols cysteine, homocysteine, and *N*-acetylcysteine using a nanocrystalline graphite-like pyrolytic carbon film electrode. These thiols or their electrochemical reaction products can cause electrode fouling. The pyrolytic carbon film was obtained by a noncatalytic thermal chemical vapour deposition method using methane as the carbon source. The electrode produced from a temperature of 1100°C proved to have superior electrochemical performance. For this electrode, the amperometric current for cysteine decreased by only 2% after 900 s (Hadi and Rouhollahi 2011). The antifouling properties of the pyrolytic carbon film is likely due to the high density of edge plane sites that promote the efficient oxidation of the thiols, and similar electrocatalytic oxygen functionalities to those on carbon hollow spheres may be present.

Polymeric films

The formation or presence of a polymeric film on an electrode surface can be detrimental to the electrode performance, such as during the analysis of phenols and neurotransmitters. However, conductive polymers have been demonstrated to show antifouling properties. For example, PEDOT was synergistically immobilised with the surfactant poly(sodium-4-styrenesulfonate) (PSS) on a glassy carbon electrode for the indirect analysis of tricresyl phosphate by detecting cresol that was formed from the hydrolysis of tricresyl phosphate (Yang et al. 2013). Using the modified glassy carbon electrode, the current after 20 repetitive measurements was 85% of the initial value, but the corresponding current was only 30% at a bare electrode. While the PEDOT polymer prevents cresol and its products from directly adsorbing on the glassy carbon electrode surface, the amphiphilic nature of PSS is also believed to aid in minimising electrode fouling by reducing the adsorption of the products of cresol (Yang et al. 2013). In another study, Pirvu and Manole (2013) used an alternative conductive polymer, polypyrrole, also with PSS to reduce fouling during the analysis of phenol. The extent of fouling was determined by surface plasmon resonance, in which the quantity of adsorbed material on the electrode surface is measured. With an ultrathin hybrid polypyrrole/PSS film on a gold electrode, the surface plasmon resonance signal was found to increase by an average of 22 m° per scan over 10 scans. Although this value indicates that the electrode was being progressively fouled, the value is significantly lower than that of a polypyrrole film electrode without PSS, where the corresponding signal increased by an average of 205 m° per scan for the first five scans and then 80 m° per scan for the last five scans. The scanning electron micrographs in Figure 4 visually show the different degrees of electrode fouling between the two electrode films. Although there is clearly less fouling with the polypyrrole/PSS film, it was not able to completely eliminate the electrode fouling. An interdigitated gold microelectrode surface was also modified with a PSS-doped polypyrrole film and used for the detection of dopamine released from pheochromocytoma (PC12) cells (Sasso et al. 2013). The modified electrode was stable under cell culture conditions for long-term amperometric experiments. In this work, the three-dimensional polypyrrole structure was speculated to decrease the freedom of movement of the protonated positively charged amino group tail of dopamine molecules and hence reduce polydopamine fouling. There could also be a combination of steric and electrostatic hindrance, limiting the intermolecular cyclisation, which is the prerequisite for the polymerisation of dopamine on an

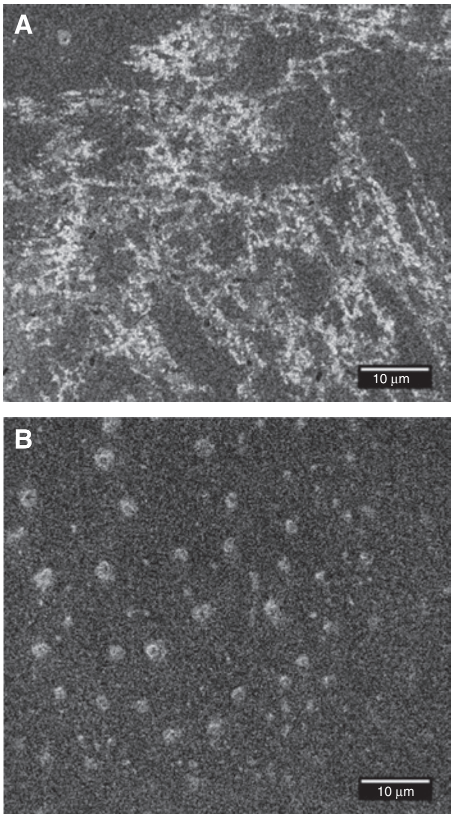


Figure 4: Scanning electron micrographs of (A) polypyrrole and (B) polypyrrole/PSS after 10 cyclic voltammetry scans in a solution of phenol.
Reproduced with permission from Pirvu and Manole (2013).

electrode surface. These results further demonstrate the greater antifouling properties of the PSS surfactant combined with conductive polymers compared to bare conventional electrodes. PSS, however, is not a requirement for an effective conductive polymer electrode. For example, for the detection of 2-(2-nitrophenyl)-1H-benzimidazole, a film of 1-naphtylamine was electropolymerised on a glassy carbon electrode surface followed by overoxidation by cycling in an aqueous sodium hydroxide solution (D'Eramo et al. 2010). Using this modified electrode, there was a 6% decrease in the reduction current after the first cycle and was then stable in subsequent cycles. At a bare electrode, however, there was a corresponding 34% decrease in current after the first cycle (D'Eramo et al. 2010). Evidently, the modified electrode was capable of reducing the extent of adsorption by the reduction product of the analyte, but the previous two conductive polymers with PSS seemed to provide greater fouling protection relative to bare conventional electrodes. This may be due to the presence of PSS or the particular analytes and fouling agents. Heterocyclic conductive polymeric films have also shown antifouling properties without the use of a surfactant such as PSS. To reduce electrode fouling, 3-amino-5-mercapto-1,2,4-triazole films were electropolymerised on glassy carbon electrodes for the detection of riboflavin, ascorbic acid, and folic acid (Revin and John 2012d), inosine (Revin and John 2012b), tyrosine (Revin and John 2012c), and norepinephrine and serotonin (Revin and John 2012a). In all analyses, there was a negligible change in current after 20 cycles with RSD values of 1.4% to 2.0%. These results indicate that electropolymerised films of heterocyclic conductive polymers can provide antifouling protection against a range of small biologically relevant molecules.

In addition to conductive polymers, nonconducting polymers may also be useful provided they are porous, allowing the analyte to reach the electrode surface while restricting the access of larger fouling agents, or mediate the electrochemical reaction on the polymer rather than the electrode surface. The polymer formed from the electropolymerisation of eugenol is known to be a nonconducting, porous polymer (Paul et al. 2013). The application of this polyeugenol coating to a gold electrode preserved the sensitivity of the electrode for oxygen detection in the presence of bovine serum albumin for 16 h (Paul et al. 2013). Without the polyeugenol coating, the sensitivity of a bare gold electrode to oxygen decreased by 80%. The pores in the polyeugenol film were too small to allow bovine serum albumin to reach the electrode surface, but oxygen was able to travel through the pores. Another nonconducting, porous polymer, chitosan, was immobilised on an electrode simply by incubating carbon fibre microelectrodes in chitosan solution for 15 s (Özel et al. 2011). The fabricated electrodes showed no decrease in signal after four consecutive measurements of serotonin. These modified electrodes were also satisfactorily used in four repeated determinations of serotonin in a live embryonic zebrafish intestine with minimum interference, while brief electrochemical reconditioning was performed between determinations. The authors observed similar current response after the four consecutive determinations. As chitosan has excellent sieving properties, the chitosan layer was likely acting as a protective barrier against the direct adsorption of biological molecules or large polymeric molecules formed during the oxidation of serotonin. To protect the underlying gold electrode surface, the electrode prepared by Milczarek (2009) relied on an adsorbed layer of iodine in addition to a nonconducting, porous polymeric film to prevent NAD^+ fouling. On top of this chemisorbed iodine layer, hydrolytic lignin was allowed to adsorb followed by the electrooxidation of the adsorbed lignin. Interestingly, lignin, a phenolic polymer, was used as part of an electrode to minimise fouling given that such polymers often rapidly cause fouling. A negligible decrease in current was observed after 45-min continuous amperometry (Milczarek 2009). Milczarek (2009) suggested that the adsorbed iodine minimised the oxidation of NADH on the surface of the gold electrode, but the oxidation of NADH was mediated by the adsorbed lignin polymeric film, thereby preventing the fouling of the electrode surface by NAD^+.

Nafion is a porous membrane that contains sulfonic acid functional groups, which gives the membrane a negative charge when exposed to an aqueous electrolyte. As an electrode coating, Nafion has demonstrated some antifouling properties due to it acting as a physical barrier to fouling agents and electrostatic repulsion of negatively charged fouling agents. Razmi and Heidari (2009) constructed a lead nitroprusside nanoparticle-modified carbon ceramic electrode coated with Nafion. Cyclic voltammetry and amperometry of 5 mᴍ and 10 μᴍ cysteine, respectively, were used to assess the performance of the electrode. The cyclic voltammetric current decreased by 12% after 10 cycles and then a further 8% after 40 cycles, and the amperometric current decreased by 10% after 10 min and then a further 5% after 20 min (Razmi and Heidari 2009). Without the Nafion coating, however, the cyclic voltammetric current decreased by 45% after 10 cycles and then a further 20% after 40 cycles, and the amperometric current decreased by 20% after 10 min and then a further 15% after 20 min (Razmi and Heidari 2009). Although nanoparticles can also have antifouling properties, these results clearly illustrate that the Nafion coating improved the fouling resistance of the electrode to cysteine and its products. As cysteine and its products can reach the electrode surface and nanoparticles by permeating the Nafion membrane, the ability of Nafion to reduce electrode fouling suggests that the fouling agent responsible may be negatively charged and is repelled by the negatively charged Nafion film.

Individual polymer chains, such as poly(ethylene glycol), can be attached to an electrode surface to provide a dense polymeric film that resists fouling by a diversity of fouling agents. To protect against protein fouling, various poly(ethylene glycol) monomethyl ether moieties were grafted on a hydrogenated silicon surface by Perez et al. (2012) to investigate the adsorption of bovine serum albumin. The modified electrode exhibited excellent antifouling properties toward bovine serum albumin after being incubated in a solution for 1 h. With grafted moieties, the chain length, rather than the number of ethylene oxide monomers, was reportedly related to the antifouling behaviour. Similarly, Zhang et al. (2009) investigated the use of oligo(ethylene glycol) thiols as an electrode coating for an electrochemiluminescent sequence-specific DNA sensor. The use of oligo(ethylene glycol) thiols was found to reduce the nonspecific adsorption of the glucose oxidase enzyme label. After incubating an oligo(ethylene glycol) thiol-modified electrode in glucose oxidase for 30 min, there was only a minimal increase in the electrochemiluminescent signal compared to the signal before enzyme incubation. On the contrary, there was a 10-fold increase in signal at a comparable electrode modified with the commonly used antifouling agent, 6-mercaptohexanol, indicating significant nonspecific adsorption of glucose oxidase (Zhang et al. 2009). In addition to neutrally charged polymer chains such as poly(ethylene glycol), charged chains can be attached to an electrode to provide fouling resistance. Li et al. (2014) have used surface-initiated photoiniferter-mediated polymerisation to guide the growth of the amino acid-based zwitterionic polymers, poly[N^4-(2-methacrylamidoethyl)asparagine] and poly[N^5-(2-methacrylamidoethyl)glutamine], on gold surfaces. Using surface plasmon resonance, the authors reported the effective resistance to nonspecific protein adsorption from human blood serum and plasma when the polymer thickness was <11 nm. Moreover, the surface was also resistant to cell adhesion after incubating these polymer-coated electrodes in a culture medium with a concentration of 10^5 cells ml^{-1} (Li et al. 2014). These polymers could be resistant to fouling due to the net balanced charge, which increases hydrophilicity without placing a net charge on the electrode surface.

Although many antifouling strategies to reduce electrode fouling have involved increasing surface hydrophilicity, this is not a feasible strategy for all applications. As an example, a hydrophobic coating is needed to reduce friction in digital microfluidics, where droplets are manipulated electrodynamically between electrodes (Sarvothaman et al. 2014). Due to the hydrophobic coating of digital microfluidics, they are prone to fouling by hydrophobic species, such as unfolded proteins. Sarvothaman et al. (2014) improved the fouling resistance of a digital microfluidics coating through the use of a fluorinated poly(ethylene glycol) and perfluorinated methacrylate copolymer. The use of the new copolymer increased the lifetime of a device from 102 to 580 actuation steps compared to the standard amorphous fluorinated copolymer, Teflon-AF, used with serum and cellular materials (Sarvothaman et al. 2014). The addition of the fluorinated poly(ethylene glycol) was suggested to increase elasticity and lubricity, which improves the fouling resistance to components in serum and cellular samples. Similarly, a hydrophobic, highly plasticised poly(vinyl chloride) membrane was used to improve the selectivity and fouling resistance of glassy carbon electrodes for the analysis of the hydrophobic compound, propofol (Kivlehan et al. 2012). The poly(vinyl chloride)-modified electrode reduced the fouling of the electrode surface by the products of the oxidation of propofol, as no decrease in the current was observed after six repetitive cycles (Kivlehan et al. 2012). Furthermore, due to the large difference in hydrophobicity of the propofol analyte and common interfering species, only the analyte of interest could penetrate the poly(vinyl chloride) membrane to be detected at the electrode surface.

Many other polymeric films can be used to protect electrodes from fouling species. Trouillon et al. (2009) investigated the performance of many polymeric membrane coatings including Nafion, cellulose acetate, chitosan, fibronectin, and PSS/poly(L-lysine) for a gold electrode in resisting fouling by bovine serum albumin. Their ability to resist fouling was evaluated by performing cyclic voltammetry of $[Ru(NH_3)_6]^{2+/3+}$ and dissolved oxygen in the presence and absence of bovine serum albumin. Based on the peak potential, peak width, peak current, and capacitance, fibronectin coating was the only membrane that was not significantly different in the presence of bovine serum albumin from a pristine bare gold electrode (Trouillon et al. 2009). All other coated electrodes showed some significant difference from a pristine bare gold electrode in the presence of bovine serum albumin, suggesting that the other membrane coatings provided less fouling protection. However, all of the tested membrane coatings provided some protection from fouling by bovine serum albumin compared to a bare gold electrode. Singh et al. (2011) also investigated several different polymeric films to prepare fouling-resistant dopamine selective sensors for detection in brain tissues. Nafion, base-hydrolysed cellulose acetate, and fibronectin-modified carbon fibre electrodes were prepared. The authors observed that approximately 70% to 80% of dopamine oxidation current was retained at all types of modified electrodes after a 2-h incubation in bovine serum albumin and brain tissue. Among the electrodes, base-hydrolysed cellulose acetate-modified electrodes were found to be most resistant to fouling. The cellulose film offers a steric barrier that prevents macromolecules from diffusing to the surface and its porosity can be progressively increased by controlled hydrolysis (Marinesco and Carew 2002).

Nonpolymeric films

Nonpolymeric thiol (mercapto) films or other sulfur-based films can be efficiently and strongly attached to gold electrodes through gold-sulfur bonds, such as the commonly used 6-mercaptohexanol, to reduce electrode fouling. However, Jolly et al. (2015) found that a 6-mercaptohexanol-modified electrode did not provide as much fouling protection as a novel sulfur-based film electrode. In this study, an aptamer-based biosensor was developed for the determination of prostate-specific antigen. On this sensor, a thiol-terminated sulfobetaine, the structure of which is shown in Figure 5, was used as an antifouling agent to reduce the fouling of the sensor by human serum albumin. After the incubation of the sensor in human serum albumin, there was a negligible change in the electron transfer resistance (R_{ct}; <1%) estimated using electrochemical impedance spectroscopy (Jolly et al. 2015). However, the use of 6-mercaptohexanol resulted in an increase of 12.5% in R_{ct} upon incubation in human serum albumin. With both the oligo(ethylene glycol) thiol-modified electrode (Zhang et al. 2009) and the sulfobetaine-modified electrode, the poorer fouling resistance of 6-mercaptohexanol may be due to its shorter chain length, which could result in a greater number of surface defects exposing the gold surface (Jolly et al. 2015). Similarly, Kuralay et al. (2011) and McQuistan et al. (2014) investigated the improvement in fouling resistance when 6-mercaptohexanol was combined with other sulfur-based materials. Kuralay et al. (2011) constructed a ternary monolayer on a screen-printed gold electrode. This ternary monolayer consisted of hexanedithiol, a specific thiolated capture probe, and 6-mercaptohexanol (HDT/SHCP/MCH electrode) and was used to detect nucleic acid hybridisation events. After 24-h incubation in serum and urine, the current was 80% to 85% of the initial value. There was a significant reduction in current and increase in noise when hexanedithiol was not used (SHCP/MCH electrode), as shown in Figure 6. The authors suggested that the use

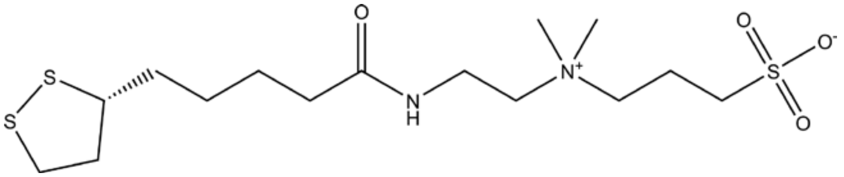


Figure 5: Chemical structure of the thiol-terminated sulfobetaine used by Jolly et al. (2015): (*R*)-3-((2-(5-(1,2-dithiolan-3-yl)pentanamido)-ethyl)dimethylammonio)propane-1-sulfonate).

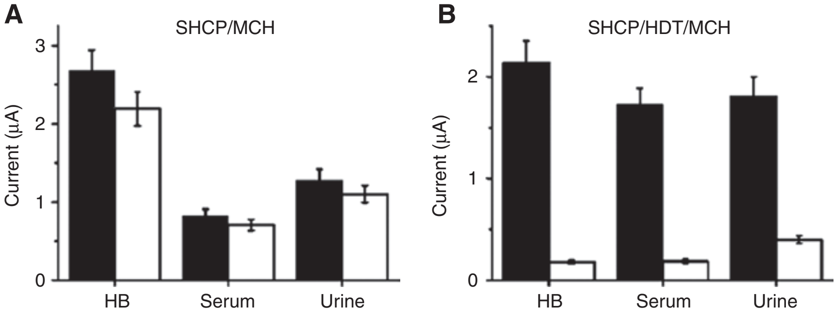


Figure 6: Antifouling properties of the SHCP/MCH electrode (A) and SHCP/HDT/MCH electrode (B) after 24 h in hybridisation buffer (HB), serum, and urine.
Black columns represent response from 1 nM of target DNA and white columns represent blank response (0 nM of target DNA). Reproduced with permission from Kuralay et al. (2011).

of hexanedithiol leads to more dense monolayers with fewer pinholes and surface defects. In addition to 6-mercaptohexanol, McQuistan et al. (2014) incorporated short thiolated oligonucleotides (containing varied numbers of thymines) as antifouling diluents in an electrochemical peptide-based sensor to minimise the nonspecific adsorption of nontarget immunoglobulin G. With the use of thiolated oligonucleotides, there was only a 5% signal suppression after being incubated in nontarget immunoglobulin G. Without the thymines (only 6-mercaptohexanol), there was significant fouling of the electrode, resulting in a 35% signal suppression. The negatively charged backbone of the oligonucleotides may help limit the electrode fouling as a result of unfavourable electrostatic interactions or increased hydrophilicity (McQuistan et al. 2014). Although these results demonstrate that 6-mercaptohexanol generally has poor antifouling properties, other sulfur-based films can be used alone or in combination with 6-mercaptohexanol to minimise electrode fouling. Instead of a thiol, Motaghedifard et al. (2012) employed a thiophene to immobilise a self-assembled monolayer of 2-hydroxy-*N*′1-[(*E*)-1-(3-methyl-2-thienyl)methylidene] benzohydrazide and used the electrode in the determination of epinephrine. The authors demonstrated excellent antifouling properties of the electrode after no change in the oxidation current of epinephrine was observed upon 20 repetitive scans.

Without the formation of gold-sulfur bonds, nonpolymeric films that do not contain thiols or similar sulfur-based functional groups must be attached to an electrode surface by other methods, such as diazonium chemistry. To protect a glassy carbon electrode from a large range of fouling agents, Chira et al. (2014) used diazonium chemistry to covalently attach 1-[(4-nitrophenyl)methyl]-4,4′-bipyridinium to the electrode surface, yielding a stable 1-phenylmethyl-4,4′-bipyridine film. Following the incubation of the modified glassy carbon electrode in solutions of bovine serum albumin, phenol, casein, riboflavin, pectin, sodium dodecyl sulfate, linoleic acid, and pepsin for 20 min, the change in R_{ct} before and after incubation was estimated to be <2.5 kΩ by electrochemical impedance spectroscopy (Chira et al. 2014). The change in R_{ct} was significantly greater at a bare glassy carbon electrode. The authors suggested that the antifouling properties of the modified glassy carbon electrode were due to the reduction of surface hydrophobicity, masking of functional groups on the electrode surface, and steric repulsion of fouling agents from the 1-phenylmethyl-4,4′-bipyridine. Similarly, Chandra et al. (2013) electrochemically deposited a *p*-phenylacetate film on conical-tip carbon electrodes using diazonium chemistry to enhance the antifouling properties of the electrodes. Their modified electrodes offered a degree of protection for carbon electrodes against fouling during dopamine detection. The modified electrode was demonstrated to retain 75% of the initial detection signal after being incubated for 7 days in a simulated fouling solution containing caproic acid (a lipid), bovine serum albumin (a protein), cytochrome *c* (a protein), and human fibrinopeptide B (a peptide) that partially mimics the environment of extracellular fluid. During their *in vivo* experiments involving Sprague-Dawley rats, 70% to 95% of the dopamine oxidation current remained after the first 40 min and 50% remained over the next 20 min, indicating that the electrodes may not be as fouling resistant as in the *in vitro* experiments. Therefore, the complex environment *in vivo* may need to be taken into consideration in the development of electrodes for *in vivo* detection.

A polymer layer that passivates an electrode surface will tend to increase the impedance. Therefore, the compromise between impedance and fouling resistance must be assessed in considering the use of such films. As an alternative, Gui et al. (2013) reported a low impedance phenyl phosphorylcholine-based zwitterionic layer immobilised on a glassy carbon electrode. Owing to the influence of the charge of proteins on fouling, the adsorption of anionic bovine serum albumin and cationic cytochrome *c* was monitored at this modified electrode by fluorescence microscopy. Although the phenyl phosphorylcholine-modified electrode demonstrated greater or similar resistance to fouling by the two proteins compared to oligo(ethylene glycol)-modified glassy carbon or gold electrodes, the impedance was much lower than that at the oligo(ethylene glycol)-modified electrodes (Gui et al. 2013). The results of this work suggest that complete charge balancing and packing of the charged groups of phophorylcholine zwitterions provided resistance to electrode fouling without creating high impedance.

Antifouling nonpolymeric films can also be attached to the surface by noncovalent interactions. Such an electrode utilising a film of electrogenerated oxidation products of NAD^+ has been shown to exhibit good antifouling properties against NAD^+ adsorption (Teymourian et al. 2012). The modified glassy carbon electrode was constructed by immobilising multiwalled carbon nanotubes dispersed in an ionic liquid on a glassy carbon electrode followed by electrooxidising NAD^+ on the electrode surface. The ionic liquid was included to bind the carbon nanotubes and oxidised NAD^+ to the electrode surface, whereas the carbon nanotubes acted as an electrical conductor between the electrode surface and the oxidised NAD^+, which served as a redox mediator (Teymourian et al. 2012). As illustrated in Figure 7, for the analysis of

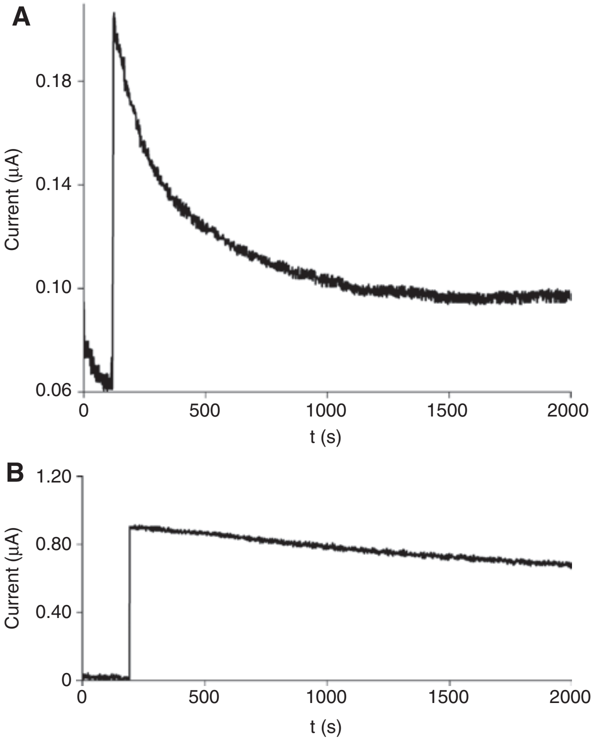


Figure 7: Amperometric response of a bare glassy carbon electrode (A) and the oxidised NAD$^+$/multiwalled carbon nanotube/ionic liquid-modified glassy carbon electrode (B) to a solution of NADH over 1800 s.
Reproduced with permission from Teymourian et al. (2012).

NADH, the current at the modified electrode decreased by 15% after 1800 s, whereas a corresponding current decrease of up to 70% was obtained at a bare glassy carbon electrode (Teymourian et al. 2012). The authors attributed the antifouling properties of this modified electrode to the improved electron transfer kinetics and more negative oxidation potential of the electrooxidised NAD$^+$ film, which reduced the formation of adsorbing radical intermediates.

Protein films and coatings

Many antifouling strategies seek to prevent a fouling agent, such as a protein, from reaching the electrode surface by establishing a barrier that is only permeable to the analyte. In some cases, the barrier that prevents fouling can actually be a protein attached to the electrode surface. The S-layer protein, SbpA, isolated from *Lysinibacillus sphaericus* CCM 2177, was used to provide an antifouling monolayer on a platinum electrode with pore sizes of 4 to 5 nm (Picher et al. 2013). After incubation in human serum albumin, human serum, and human blood, the corresponding mass density of adsorbed molecules was measured to be 0, 0.18, and 0.46 ng mm^{-2} on the electrode surface by surface plasmon resonance. The SbpA layer substantially reduced the electrode fouling compared to a bare gold electrode as well as poly(ethylene glycol) and bovine serum albumin coatings (Picher et al. 2013). In addition to the greater fouling resistance, pores in the SbpA layer allow small analytes to reach the electrode surface while excluding large fouling agents, unlike poly(ethylene glycol) and bovine serum albumin coatings. Protein films or coatings can also be immobilised on an electrode surface to impart targeted functionalities or properties. For example, Qiu et al. (2013) constructed a horseradish peroxidase-modified nanostructured gold thin-film electrode for the analysis of 4-chlorophenol. The presence of horseradish peroxidase significantly improved the fouling resistance with 81.5% of the initial current remaining after 30 cycles compared to a corresponding 9.9% at a bare gold thin film (Qiu et al. 2013). The presence of the horseradish peroxidase has likely increased fouling resistance because the phenol oxidation does not occur directly on the gold electrode surface and the enzyme provides a physical barrier against the adsorption of the phenol or reaction products on the surface.

Metallic nanoparticles and catalytic redox couples

The nanoscale size of metallic nanoparticles imparts useful electrocatalytic properties as well as a high electrical conductivity (Safavi and Momeni 2010, Muna et al. 2014). Nanoparticles have also been shown to exhibit antifouling properties and may be used alone or in combination with other materials. Indeed, Safavi and Momeni (2010) combined gold nanoparticles with a carbon ionic liquid electrode. This electrode was shown to be resistant to fouling by the products of tryptophan, as there was only a slow decrease in oxidation current over five cycles. This fouling resistance was somewhat greater than a bare ionic liquid carbon paste electrode and much greater than a bare glassy carbon electrode or conventional carbon paste electrode, both of which showed rapid electrode fouling (Safavi and Momeni 2010). The antifouling properties of the modified electrode could be attributed to the particular electrocatalytic properties of the gold nanoparticles, which mediated the electrochemical reactions. The polarity of the ionic liquid may have also contributed by increasing the surface hydrophilicity.

Similarly, Adams et al. (2010) combined a sol-gel network of (3-mercaptopropyl)trimethoxysilane (MPTS) with gold nanoparticles to measure dopamine secreted during single-cell exocytotic events in PC12 cells. In fabricating these electrodes, gold was electrochemically deposited on carbon fibre microdisc electrodes before the deposited gold was chemically functionalised by MPTS for 20 min. Subsequently, gold nanoparticles were immobilised on a thiol-terminated three-dimensional sol-gel network of MPTS. The fabricated electrode was stored for both short term (2–10 days) and long term (38–46 days) after the amperometric detection of dopamine in PC12 cells. At the end of both storage durations, the measured current remained fairly constant without any electrode pretreatment, indicating a low level of fouling during exposure to PC12 cells. The sol-gel network of MPTS on the electrode surface was proposed to have formed a barrier towards cellular debris adhesion and direct molecular adsorption on the electrode surface. The electrocatalytic and antifouling properties of the gold nanoparticles would also have contributed to the observed resistance to fouling. For the analysis of norepinephrine and dopamine, aminophenyl grafted gold nanoparticles on glassy carbon electrodes provided good protection from the polymeric fouling products of the neurotransmitters. Kesavan et al. (2012) immobilised β-ᴅ-glucose-capped gold nanoparticles on an aminophenyl grafted glassy carbon electrode and used the electrode to detect norepinephrine in the presence of uric acid. This modified electrode demonstrated antifouling properties against norepinephrine after 15 repetitive measurements at 5-min intervals. Similarly, Kesavan and John (2014) prepared a layer of aminophenyl grafted gold nanoparticles on a glassy carbon electrode without capping the nanoparticles with β-ᴅ-glucose. In addition to an enhancement of the oxidation of dopamine, the authors also found the electrode to be resistant to fouling caused by the oxidation products in 15 repeated scans, which suggests that capping the nanoparticles does not improve the fouling resistance of the electrode. Alternatively, Guo et al. (2014) constructed a palladium-nickel bimetallic alloy nanoparticle-modified carbon nanofibre electrode, in place of monometallic nanoparticles, to exploit the generally higher electrocatalytic activity, selectivity, and stability of bimetallic alloy nanoparticles (Guo et al. 2014). This electrode was constructed by electrospinning a solution of polyacrylonitrile, palladium(II) acetylacetonate, and nickel(II) acetylacetonate followed by the reduction of the metals and carbonisation of the polyacrylonitrile fibres by a controlled thermal process. Coupled with flow injection analysis, the electrode showed a minimal decrease in current after 60 injections of glucose (RSD 1.45%). For a bare nickel electrode, the current decreased by 38% after 60 injections (RSD 10.3%; Guo et al. 2014). These results demonstrate that the electrode exhibits a good resistance to fouling by the products of glucose oxidation and this could be attributed to improved electrocatalytic and antifouling properties from the synergistic effect of nanoscale palladium and nickel. Maiyalagan et al. (2013) also prepared an electrode by electrospinning and carbonisation, which appeared to induce the formation of small crystalline α-Fe_2O_3 nanoparticles on the surface of carbon nanofibres. This α-Fe_2O_3 nanofibre-modified glassy carbon electrode showed good resistance to fouling by the products of folic acid during its analysis. After 20 cycles in a solution of folic acid, there was a negligible change in current (RSD 2.1%) at the modified electrode. On the contrary, at a bare glassy carbon electrode and bulk Fe_2O_3 electrode, the oxidation peak of folic acid continuously decreased after each cycle (Maiyalagan et al. 2013). This difference in fouling resistance is likely due to the presence of nanoparticles with the particular crystal structure of α-Fe_2O_3, which catalyses the efficient oxidation of folic acid, minimising the adsorption of fouling species.

Similar to nanoparticles, metallic redox couples can exhibit important electrocatalytic properties and resistance to electrode fouling. Both Muna et al. (2014) and Safavi et al. (2009) investigated the electrocatalytic and antifouling properties of the $Ni(OH)_2$/NiOOH redox system. Coupled with flow injection analysis, Muna et al. (2014) detected estrone (a phenolic steroid) at a nickel nanoparticle-modified glassy carbon electrode and observed a negligible change in the current after 20 consecutive injections of estrone (RSD 0.5%). The authors attributed the fouling resistance to the catalytic $Ni(OH)_2$/NiOOH redox system, which forms on the electrode surface after cycling in alkaline electrolyte. Safavi et al. (2009) combined the catalytic $Ni(OH)_2$/NiOOH redox couple with graphite and an ionic liquid to produce an antifouling electrode for the detection of glucose (Safavi et al. 2009). The $Ni(OH)_2$ nanoscale carbon ionic liquid composite electrode exhibited good antifouling properties with six repetitive amperometric measurements having an RSD of 3.4%. The current and peak potential of repetitive cyclic voltammetric scans did not change, which also showed that the electrode did not foul (Safavi et al. 2009). Similar to Muna et al. (2014), the observed antifouling properties of this composite electrode are likely due to the nickel redox couple, but the presence of the ionic liquid could also have contributed to the fouling resistance by increasing the hydrophilicity of the electrode.

Nanoporous electrodes

Nanoporous electrodes have numerous nanoscale pores through the electrode structure that are separate from the bulk solution, but diffusion from the bulk solution into the pores is possible for species of a defined size. Nanoporous electrodes have been demonstrated to show a higher fouling resistance than planar electrodes; however, the observed antifouling properties strongly depend on the size of the pores. To investigate the relationship between pore size and electrode fouling, Patel et al. (2013b) investigated the performance of planar, macroporous (1200 nm pore size), hierarchical (1200 and 60 nm pore size), and nanoporous (<50 nm pore size) gold electrodes in the presence of bovine serum albumin and fibrinogen. As expected, the antifouling performance of these electrodes was found to be highly dependent on the pore size, with the nanoporous electrode having the greatest fouling resistance (Patel et al. 2013b). Figure 8 shows cyclic voltammograms obtained over the course of 60 min in the presence of bovine serum albumin. Clearly, the nanoporous electrode offers the greatest protection, with only a small decrease in current and a small increase in peak separation. The antifouling properties of nanoporous electrodes appear to be due to their high surface area and nanoporosity. While fouling agents in the bulk solution can readily adsorb on the gold surface in contact with the bulk solution, fouling of the inner surfaces would be slower due to restricted mass transport of larger species through small pores in the nanoporous electrode. With the other porous electrodes, there were sufficiently large pores for bovine serum albumin to reach the inner electrode surface, indicating that a pore size of <50 nm is required for fouling resistance to bovine serum albumin and similar-sized proteins. Fouling by smaller proteins and protein fragments can also be greatly minimised with the use of nanoporous electrodes, as illustrated by Summerlot et al. (2011) using fragmented amyloid-β protein. After a 30-min incubation in a protein solution, the current at a nanoporous gold electrode decreased by only 13%, whereas the current at a planar bare gold electrode decreased by 96.5% (Summerlot et al. 2011). Although the experiment was conducted for 30 min, the electrodes reached the above values within ~10 and 2 min for the nanoporous and planar electrodes, respectively. Despite the fragmented amyloid-β proteins being smaller than most proteins (e.g. albumin), the pores are still sufficiently small to restrict the fragmented proteins without affecting analyte detection. Similarly, Quynh et al. (2014) showed that a nanoporous gold electrode could resist fouling by the polymeric oxidation products of aniline and hydroxylamine. This electrode was prepared by dealloying silicon from an Au_xSi_{1-x} film. After five repetitive measurements, a maximum of 10% deviation in current was observed. In contrast, a bare planar gold electrode was fouled even after only one measurement. Due to the nanoporosity of the electrode, the analysis of small analytes can continue even if the very outer surface is fouled. In this case, as the analytes aniline and hydroxylamine can reach the inner surfaces of the

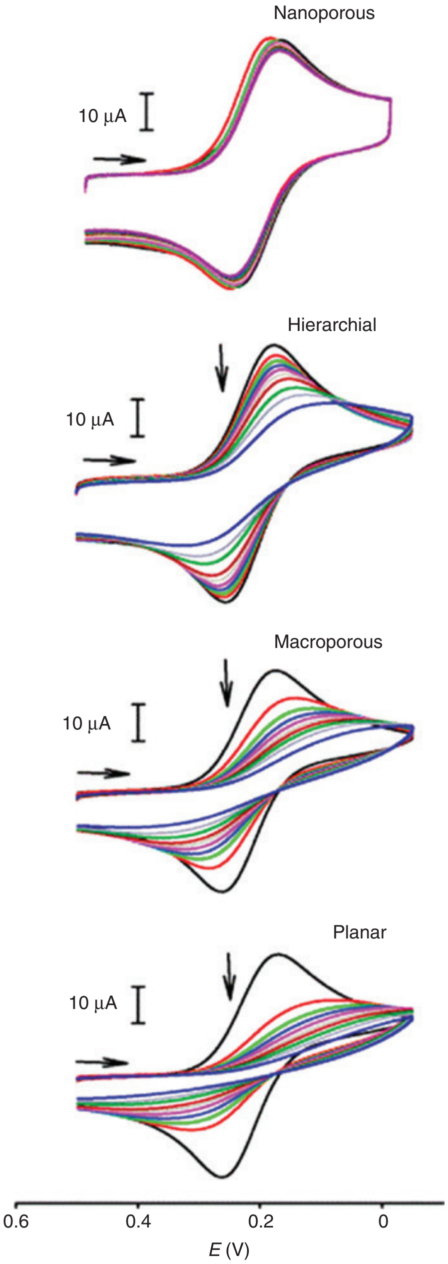


Figure 8: Cyclic voltammograms at nanoporous, hierarchical, macroporous, and planar gold electrodes in a solution of ferricyanide and bovine serum albumin.
Cyclic voltammograms were obtained between ~1 and 60 min. Reproduced with permission from Patel et al. (2013b).

nanoporous electrode, the polymeric oxidation products may even be deposited within the pores. Although five satisfactory repetitive measurements could be obtained, the nanoporous electrode may have become fouled with additional use if the oxidation products could not diffuse out of the nanoporous structure before polymerisation.

In addition to these bare nanoporous gold electrodes, a nanoporous gold electrode can be coated to change the particular properties of the electrode. Tavakkoli and Nasrollahi (2013) combined the catalytic properties of palladium with the fouling resistance of a nanoporous gold electrode for the analysis of glucose. After 15 repetitive cycles with the palladium-coated nanoporous gold electrode, there was a negligible change in current. To demonstrate the fouling resistance of the electrode to glucose products, a bulk palladium electrode was also tested and was found to be rapidly fouled (Tavakkoli and Nasrollahi 2013).

Other effective electrode modifications

Coatings, films, or membranes can be used on an electrode to separate the susceptible electrode surface from fouling agents in the bulk solution. More simply, the distance between the electrode surface and the bulk solution can be increased with the use of a recessed electrode. Anastasova et al. (2012) combined recessed electrodes with polyurethane membranes to minimise electrode fouling by bovine serum albumin. These recessed electrodes were prepared by etching gold inside a fused silica capillary to the required depth and finally coating with polyurethane. Anastasova et al. (2012) observed that greater fouling resistance could be gained by increasing the recess depth of an electrode. After incubation with bovine serum albumin for 17 h, the reduction in oxygen response was 6±0.4% at an 880 μm recess electrode, and the reduction in glucose response was 11±0.5% at a 546 μm recess electrode both with polyurethane membranes. The benefit of using a recessed electrode was illustrated by comparing to planar electrodes. The authors observed a 45±2.7% reduction in oxygen response at a bare planar electrode and 13±1.4% at a membrane planar electrode as well as a 48±2.3% reduction in glucose response at a bare planar electrode and 17±1.2% at a membrane planar electrode. These results demonstrate that the polyurethane membrane alone has reasonable antifouling properties but, in combination with the recessed electrode, fouling by bovine serum albumin is further reduced. Although the fouling resistance of recessed electrodes is likely a result of the greater separation between the electrode surface and the bovine serum albumin in the bulk solution, the delay in signal response increases with greater recess depth.

Electrodes can be made more hydrophobic without using carbon-based materials, such as diamond and electron cyclotron resonance-sputtered nanocarbon. The hydrophobicity of the carbon paste electrode prepared by Safavi et al. (2010) was increased using the chromatography stationary phase, SE-30, as the carbon paste binder instead of an organic oil or liquid. The antifouling properties of this carbon paste electrode were investigated by amperometry in a solution of NADH. After 10 min, a 15% decrease in the oxidation current was observed at the carbon paste electrode, whereas a conventional carbon paste electrode produced a corresponding current reduction of up to 80% (Safavi et al. 2010). The fouling resistance of the modified carbon paste electrode could be a result of the low surface energy and hydrophobicity of the SE-30 binder, which reduced the adsorption of NAD^+. Zhuiykov and Kalantar-zadeh (2012) prepared an even more hydrophobic surface with a superhydrophobic 20 mol% Cu_2O-doped RuO_2 electrode ($Cu_{0.4}Ru_{3.4}O_7$+RuO_2), which was shown to exhibit high fouling resistance against biological materials. Following a 3-month field trial in a sewerage environment, the extent of electrode fouling was examined by scanning electron microscopy and potentiometry. The scanning electron micrographs showed that there was negligible fouling by biological material, and potentiometry determined that the sensitivity to oxygen detection only decreased from -46 to -43 mV decade^{-1} (Zhuiykov and Kalantar-zadeh 2012). Although a hydrophobic electrode surface can be considered prone to fouling, this superhydrophobic electrode demonstrated good resistance to fouling. Similar to the electron cyclotron resonance-sputtered nanocarbon film used by Xue et al. (2012), surface roughness or smoothness was considered to contribute to the observed antifouling properties of the superhydrophobic electrode.

Analogous to nanoporous electrodes, Mudrinić et al. (2014) developed a micropore electrode with antifouling properties by polymeric phenol products. They used bentonite clay as part of an electrode coating with carbon black and Nafion on a glassy carbon electrode. The bentonite clay was modified by pillaring, which allowed particular metal cations to be incorporated into the clay. The electrode constructed with a pillaring solution containing 90 mol% Al^{3+}, 5 mol% Fe^{3+}, and 5 mol% Ni^{2+} was shown to exhibit the highest fouling resistance. The Fe-to-Ni proportion was also shown to have an important effect on the fouling resistance. The current density at this electrode decreased by 5.4% after the first 10 cycles and 17.8% after 20 cycles (Mudrinić et al. 2014). The authors suggested that the antifouling properties may be due to a specific Al-Fe-Ni pillar structure that does not favour the formation of polymeric structures. Similarly, Hasanzadeh et al. (2013) applied silica-based mesoporous materials to the simultaneous determination of dopamine and serotonin. In their work, porous mobile crystalline material-41 functionalised by amine was immobilised on a glassy carbon electrode. A 1.2- and 3-fold enhancement in the electron transfer kinetics of dopamine and serotonin, respectively, was achieved at the modified electrode. Moreover, seven successive differential pulse voltammetric scans of 10 nM dopamine and 2 nM serotonin showed similar oxidation peak currents (RSD 3.2% and 2.0%, respectively). The fabricated electrodes also demonstrated antifouling properties during the analysis of dopamine and serotonin spiked in human serum, and the recovery of both analytes was 94% to 100% (Hasanzadeh et al. 2013). The micropores and mesopores present in the modified electrodes may have acted similarly to other porous electrodes and excluded potential fouling agents from the inner pore structures.

In an effort to reduce electrode fouling by NAD^+, Chumbimuni-Torres and Wang (2009) used a copper-ion selective electrode with potentiometric detection. The concentration of NADH was measured by monitoring the NADH-mediated reduction of copper ions in the presence of gold nanoparticle seeds. The amperommogram obtained at a bare glassy carbon electrode, depicted in Figure 9A, shows that the current decreased by 75% over the course of a continuous 50-min experiment as a result of fouling by NAD^+. On the contrary, the corresponding potentiometric response obtained at the copper-ion selective electrode, depicted in Figure 9B, shows a negligible change in the measured potential (Chumbimuni-Torres and Wang 2009). Although the greater fouling resistance of the copper-ion selective electrode may be due to the copper-ion selective membrane preventing the adsorption of NAD^+ on the underlying electrode surface, a combination of the membrane, gold nanoparticles, and reduction of copper ions might be required to yield the observed resistance to electrode fouling.

Electrochemical activation

Electrochemical activation involves the use of single anodic and/or cathodic potentials or a train of pulses to periodically clean the electrode surface. Depending on the particular conditions of the electrochemical activation, adsorbed material may be removed or the surface chemistry can be altered to reduce the adsorption of fouling agents. For example, Dejmkova et al. (2009) employed electrochemical activation to remove adsorbed material during the analysis of the phenolic flavanol, quercetin, at a boron-doped diamond electrode. The application of anodic and cathodic activation pulses (up to ±3 V) before each cyclic voltammetric scan achieved an RSD of <2% after 10 repetitive cycles of quercetin. An identically treated glassy carbon electrode suffered from continuous signal drift due to electrode fouling. Similarly, Kiran et al. (2013) found that anodic and cathodic activation pulses could be applied to remove fouling resulting from contact with urine. After placing a boron-doped diamond electrode in human urine, the electron transfer rate constant (k_0) for ferricyanide/ferrocyanide was reduced to <0.001 cm s^{-1}, indicating significant fouling of the electrode surface by components in urine (Kiran et al. 2013). By applying a set of 150 current pulses of alternating amplitude, k_0 was restored to >0.2 cm s^{-1}, which is a similar value to that of the pristine electrode (0.27 cm s^{-1}; Kiran et al. 2013). Anodic and cathodic activation pulses

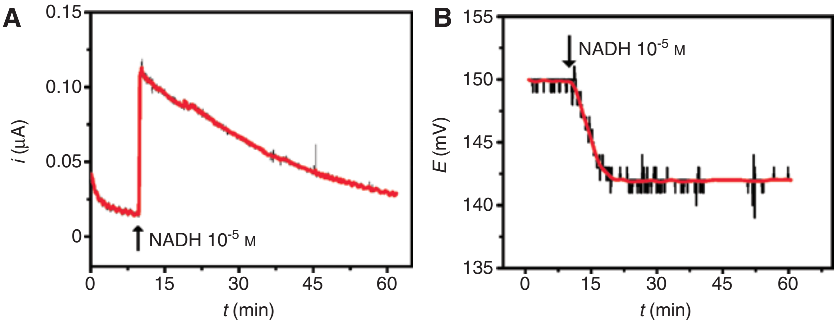


Figure 9: Amperometric response of a bare glassy carbon electrode (A) and potentiometric response of the copper-ion selective electrode (B) to a solution of NADH over 60 min.
Reproduced with permission from Chumbimuni-Torres and Wang (2009).

have also been used to remove serotonin and biological fouling agents from a boron-doped diamond electrode. Duran et al. (2014) anodically treated the electrode at 250 mA cm^{-2} for 30 s and then cathodically treated at 250 mA cm^{-2} for 180 s to activate fouled electrodes. This electrochemical activation was also capable of reactivating fouled electrodes *in situ*. To investigate this, a pristine and a fouled (after incubating in 100 μM serotonin) electrode were positioned in the extracellular space of the enterochromaffin cells in mouse ileum to detect the stimulated release of serotonin. The fouled electrode yielded a chronoamperometric signal half the magnitude of that obtained at the pristine electrode. Only by cathodically treating the fouled electrode were the authors able to achieve a signal of comparable magnitude to that at the pristine electrode. The large positive and negative potentials used in electrochemical activation can generate reactive oxygen species, such as hydroxyl radicals, as well as oxygen or hydrogen gas (Stoytcheva et al. 2014). The evolution of gas and reactive oxygen species helps to physically dislodge and oxidise adsorbed organic material, respectively.

By incorporating electrochemical activation as part of the analysis procedure, the effects of fouling can be sufficiently minimised to achieve reliable measurements. For example, by exploiting pulsed amperometry and differential pulse voltammetry, electrochemical activation can be performed at regular intervals to minimise the accumulation of a fouling layer on the electrode. This was demonstrated by Stoytcheva et al. (2014), where an anodic activation potential of +1.40 V was applied as part of a pulsed amperometric analysis of catechol at a graphite electrode. Based on five measurements of catechol, they estimated an RSD of 2.97% compared to 6.53% without the activation potential (Stoytcheva et al. 2014). da Silva et al. (2013) similarly examined the effect of an electrochemical activation potential in reducing electrode fouling during differential pulse voltammetry and multiple pulse amperometry analysis of the pharmaceutical drug, nimesulide. There was a negligible change in current after three scans by applying electrochemical activation before each scan (RSD 1.52%), but the corresponding current decreased by 16.6% without electrochemical activation (da Silva et al. 2013). Also, with multiple pulse amperometry and flow injection analysis, there was a negligible change in current after 14 injections (RSD 1.02%). However, a corresponding 15% current decrease was estimated when single potential amperometry was conducted (da Silva et al. 2013). To reduce analysis time with multiple pulse amperometry, a new two-step potential waveform (activation potential -2.0 V and detection potential +0.2 V) was employed in conjunction with flow injection analysis in the detection of carbohydrates at a gold electrode and compared to the conventional four-step potential waveform (activation potential -2.0 V, gold oxidation and reduction potentials +0.6 and -0.1 V, and detection potential +0.2 V; Kotnik et al. 2011). After 60 injections of glucose, there was a negligible change in current for both the two-step (RSD 0.16%) and four-step (RSD 0.18%) pulsed amperometric detection, demonstrating that a short cathodic pulse in the two-step detection was sufficient to activate the electrode (Kotnik et al. 2011). A careful selection of the fast scan voltammetry parameters has avoided electrode fouling during the measurement of serotonin. Agnesi et al. (2009) found that the use of a wireless instantaneous neurotransmitter concentration system comprising fast scan cyclic voltammetry from a resting potential of +0.2 to +1.0 V and then to -0.1 V and back to +0.2 V at a rate of 1000 V s^{-1} yielded a constant oxidation current amplitude after 10 sequential injections of serotonin. Subsequently, serotonin was measured using the same waveform after electrically stimulating the dorsal raphe nucleus of rat brain slices and the results indicated that high electrode sensitivity was retained throughout the measurement. Similarly, Schmidt et al. (2014) developed a modified sawhorse waveform with two different anodic scan rates and a short holding period at the switching potential to minimise fouling. The authors detected the small peptide, methionine-enkephalin, in the presence of interfering species without electrode fouling caused by the products of the peptide oxidation. Coupled with flow injection analysis, a negligible change in current was observed after 10 injections compared to a corresponding ~10% current decrease when a more conventional triangular waveform was used (Schmidt et al. 2014). As part of the modified waveform, +1.2 V was applied for only 3 ms, which must have been sufficiently anodic to remove any adsorbed material.

By applying a high anodic or cathodic potential, the surface chemistry of an electrode can be altered because of the different number of oxygen functionalities, which affects hydrophilicity. Roeser et al. (2013) and Brocenschi et al. (2014) both cathodically pretreated boron-doped diamond electrodes to modify the surface chemistry and minimise electrode fouling. During the electrochemical oxidation and cleavage of the tripeptide leucine-phenylalanine-leucine, a significant adsorption of the products of the tripeptide, including dimers, was found on a glassy carbon electrode (Roeser et al. 2013). In contrast, a boron-doped diamond electrode exhibited a more satisfactory performance, albeit the oxidation yields decreased to 20% to 30% after several days of use from an initial yield of 60% to 70%. Fouling resistance of the boron-doped diamond electrode was found to be further increased by the cathodic pretreatment of the electrode. Subsequently, there was no significant change in oxidation yield or performance after 24-h operation (Roeser et al. 2013). Similarly, Brocenschi et al. (2014) estimated RSDs of 9.6% for estrone, 11.4% for 17-β-estradiol, and 10.8% for estriol at a cathodically pretreated boron-doped diamond electrode upon 20 injections. Despite the high RSDs, the authors emphasised that these should be considered as the worst-case values, as an RSD of 2.3% was measured for estrone from 10 injections. In such work, the cathodic treatment of boron-doped diamond electrodes increases the H-termination and hydrophobicity, which would reduce the adsorption of small polar peptides and the oxidised steroid products, provided that they were sufficiently polar.

In addition to altering the surface chemistry, the application of high anodic or cathodic potentials can aid in exposing a pristine surface. Takmakov et al. (2010) electrochemically etched carbon fibre microelectrodes using cyclic voltammetry between -0.4 and 1.3 V at 400 V s^{-1} for 15 min to constantly regenerate a fresh carbon surface. The sensitivity could be restored even after an intensive fouling of electrode surfaces with dopamine. The authors used electrochemical etching to exfoliate graphite oxide and carbon particle to generate new active sites for use in subsequent experiments. This method of reactivating electrodes will keep the electrodes active *in vivo* in a prolonged experiment, as the electrodes can be regenerated by a simple electrochemical procedure *in situ*.

Although Hu et al. (2011) did not use electrochemical activation to clean an electrode surface, they instead used an analogous process to treat already fouled carbon-doped TiO_2 nanotube arrays. This process involved irradiating the electrode surface with ultraviolet and visible radiation, which is similar to electrochemical activation in that a clean electrode surface is generated by removing adsorbed fouling species. These electrodes were prepared by rapid annealing in argon as-anodised TiO_2-nanotube arrays that were deliberately fouled after obtaining featureless voltammograms at the end of 20 cyclic voltammetric scans of serotonin. The authors were able to reactivate the electrodes and achieve the original detection using ultraviolet and visible irradiation for 30 and 120 min, respectively, in doubly distilled water at room temperature. This work has demonstrated the application of ultraviolet or visible radiation to decompose the intermediate products of serotonin adsorbed on an electrode surface into H_2O, CO_2, and NO_x without damaging the surface microstructure and is analogous to applying high anodic or cathodic potentials to chemically degrade material adsorbed on the electrode surface.

Electrolyte and flow systems

The composition of the electrolyte can be modified to remove adsorbed fouling agents during electrochemical analysis. Both Anandhakumar et al. (2010) and Narmadha et al. (2011) investigated different electrolyte compositions to solubilise polymeric products from the electrochemical analysis of phenols, reducing adsorption on the electrode surface. Anandhakumar et al. (2010) compared aqueous sodium hydroxide, aqueous sodium hydroxide-sodium dodecyl sulfate micellar solution, and sodium dodecyl sulfate/hexane/butanol/water microemulsion in the analysis of several chlorophenols at a glassy carbon electrode. The authors found that, with aqueous sodium hydroxide, fouling was apparent at a 2,4-dichlorophenol concentration lower than 2 mᴍ. On the contrary, no fouling was observed up to 10 and 20 mᴍ 2,4-dichlorophenol with the micellar solution and microemulsion, respectively. The micellar solution and microemulsion were expected to solubilise the phenols and intermediates, as well as the surfactant forming adsorbed layers on the electrode, which reduces the extent of electrode fouling. Similarly, Narmadha et al. (2011) investigated the fouling resistance of acidic methanol, acidic aqueous, neutral microemulsion, and acidic microemulsion electrolytes for the oxidation of phenols at glassy carbon and boron-doped diamond electrodes. Narmadha et al. (2011) found that the acidic methanol electrolyte provided the greatest fouling resistance. For the acidic methanol electrolyte, the ratio of anodic peak current after four cycles compared to the first cycle (I^4_{pa}/I^1_{pa}) is shown in Table 1. These results show

Table 1: I^4_{pa}/I^1_{pa} values for selected phenols at a glassy carbon electrode and a boron-doped diamond electrode with an acidic methanol electrolyte (Narmadha et al. 2011).

	Electrode	2,6-Dichlorophenol	2,6-Dimethylphenol	2,6-Dimethoxyphenol
I^4_{pa}/I^1_{pa}	Glassy carbon electrode	0.94	0.99	0.98
	Boron-doped diamond electrode	0.93	0.82	0.99

that, under the experimental conditions, glassy carbon electrodes exhibited ~20% greater fouling resistance against 2,6-dimethylphenol than boron-doped diamond electrodes, although boron-doped diamond electrodes are often regarded as having greater fouling resistance compared to glassy carbon electrodes (Shin et al. 2005, Narmadha et al. 2011). In light of these results, Narmadha et al. (2011) recommended the use of a glassy carbon electrode instead of a boron-doped diamond electrode because the glassy carbon electrode can be easily cleaned by mechanical polishing. The more satisfactory performance of the acidic methanol electrolyte is most likely due to the greater solubility of the phenols and their products in the organic solvent.

In addition to aqueous/nonaqueous solvents and surfactants, the effect of supporting electrolyte salts in minimising electrode fouling has also been studied. Two electrolyte salts were investigated for use in the complete mineralisation of trichloroethene at a Ti/IrO_2-Ta_2O_5 electrode (Lakshmipathiraj et al. 2012). Using Na_2SO_4, the current changed between the first two cycles, but there was only a minimal change in current in the subsequent four cycles. On the contrary, using $NaNO_3$, the current decreased after every cycle. The higher fouling resistance associated with Na_2SO_4 was attributed to the *in situ* generation of sulfur-based oxidants, such as $S_2O_8^{2-}$ and SO_4^{2-}, which would remove material adsorbed on the surface of the electrode (Lakshmipathiraj et al. 2012). Such oxidant generation was not believed to occur when $NaNO_3$ was used (Lakshmipathiraj et al. 2012).

The contact between a susceptible electrode and fouling agents can be minimised or even eliminated in some cases through the use of a flow system. To reduce the adsorption of enzymes to electrode surfaces, Godino et al. (2010) developed a novel zero dead volume rotary switch valve that allowed for the enzyme β-galactosidase and the electrode to be separated at all stages of the assay. This involved immobilising the enzyme on streptavidin-coated magnetic particles and removing nonspecifically bound enzyme before introducing the substrate. When the electrode was directly incubated with the enzyme solution for 10 min, the background current increased from 3.5 to 8 nA. As the enzyme and the electrode never come into contact, there is no possibility for fouling of the electrodes by the enzyme, which is the most ideal solution to electrode fouling. However, it is not possible to completely separate the electrode from fouling agents in most situations. Instead of preventing the electrode from coming in contact with fouling agents, Casella and Contursi (2012), Tormin et al. (2014), and Sansuk et al. (2012) used flow systems to minimise the adsorption of fouling agents. Casella and Contursi (2012) used a cobalt oxide/oxyhydroxide redox couple (CoO_2/CoOOH)-modified glassy carbon electrode to resist fouling during the electrooxidation of hydrazines. Under stirring chronoamperometric conditions, the current at the modified electrode decreased very rapidly after the addition of phenylhydrazine owing to rapid fouling by the analyte (Casella and Contursi 2012). However, using the same modified electrode with flow injection analysis, a negligible change in oxidation current of both phenylhydrazine and hydrazine was achieved over multiple injections. While a similar redox couple to the previously reported $Ni(OH)_2$/NiOOH was used (Safavi et al. 2009, Muna et al. 2014), the observed resistance to fouling involving CoO_2/CoOOH was likely due to more efficient desorption of analytes and products from the electrode surface under flowing conditions as well as to the continuous electrodeposition of new cobalt oxide/oxyhydroxide species to replace lost or poisoned species (Casella and Contursi 2012). Continuous electrodeposition was possible because the detection and deposition potentials were similar and cobalt-gluconate complex was present in solution. Similar to flow injection analysis, batch injection analysis is a simpler version without the tubes, pumps, and injection valves. A batch injection analysis system combined with carbon screen-printed electrodes modified with graphene has been used for the detection of diclofenac (Tormin et al. 2014). There was a minimal decrease in the oxidation current after 10 runs (RSD 1.3%), as shown in Figure 10. Under steady-state conditions with square wave voltammetry, however, Figure 10 illustrates that the current decreased rapidly over the first six runs and was highly variable in subsequent runs (RSD 6.2%). In their work, the authors exploited the injection of

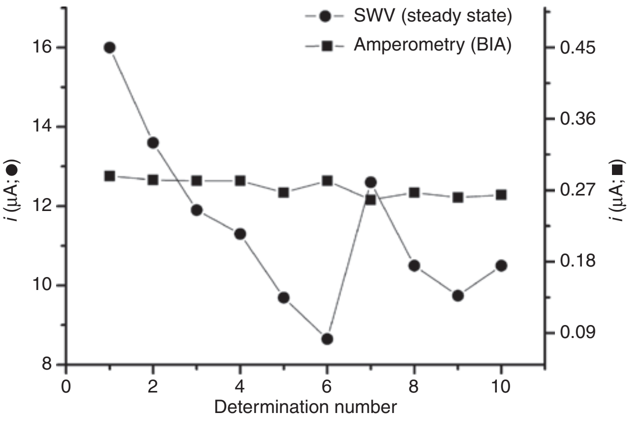


Figure 10: Current data over 10 runs of a solution of diclofenac using square wave voltammetry (steady-state conditions; •) and batch injection analysis with amperometry (■).
Reproduced with permission from Tormin et al. (2014).

a minimum solution volume under a high dispensing rate with constant stirring to reduce fouling by the products of diclofenac (Tormin et al. 2014). Sansuk et al. (2012) also used a small sample volume and high flow rate to minimise fouling. They employed single-walled carbon nanotubes as an amperometric detector in a microfluidic cell for dopamine. In this work, these electrodes showed no fouling over the concentration range of 5 to 1000 nᴍ for a period of 20 days. The absence of fouling was attributed to the relatively fast continuous flow of electrolyte (1 ml min^{-1}) that sweeps possible fouling products away from the electrode surface and also the small volume of analyte in contact with electrode. Notably, the electrode was only in contact with a very small volume of dopamine (50 μl) for a short period of time. Polymer growth from dopamine is a slow step process that may take longer than the residence time of the analyte around the fabricated fluidic cell (Harreither et al. 2013).

Conclusion

Electrode fouling can often complicate the electrochemical analysis of many analytes, particularly those of biological and medical interest. Fouling agents, such as proteins, phenols, and neurotransmitters, can adsorb on the surface of unprotected electrodes, giving rise to deteriorating transient detection signals and thus strongly affect the performance of the electrochemical technique or sensor.

Many antifouling strategies have been discussed in this review. However, more research into antifouling strategies is needed to minimise the impact of electrode fouling in practical applications. Due to the diversity of analytes that foul electrodes and the abundance of other fouling agents in some samples, care should be taken when interpreting results where a decrease in signal is observed with repeated analysis as electrode fouling may be a cause. Therefore, antifouling strategies should be tested against a variety of fouling agents and fouling matrices, particularly biological samples and matrices, which can be a complex and often unknown mixture of proteins, peptides, lipids, and carbohydrates. However, when testing the fouling resistance of a particular strategy, sometimes only one analyte, such as phenol, or one protein, such as bovine serum albumin, is investigated. Although these may be representative fouling agents, it does not indicate how the antifouling strategy will perform in more complex environments. Where possible, antifouling strategies should be tested against the widest variety of fouling agents and complex matrices appropriate to the intended application, for example, different chlorophenol isomers and blood, serum, or urine. Similarly, the relationship between fouling agent concentration and extent of fouling should not be overlooked, as fouling can occur with some antifouling strategies above a certain concentration.

The majority of antifouling strategies involve modifying the electrode with a coating or film to increase fouling resistance. Carbon-based materials, such as carbon nanotubes and graphene, are commonly used due to their large surface area, electrical conductivity, and electrocatalytic properties (Shan et al. 2009, Zhou et al. 2009, Gasnier et al. 2012, Teymourian et al. 2012). Although research into the antifouling properties of such materials should be continued, new carbon-based materials must also be investigated, as they may be resistant to fouling. For example, electron cyclotron resonance-sputtered nanocarbon (Kato et al. 2011, Xue et al. 2012) and carbon double-shelled hollow spheres (Gao et al. 2011) have been shown to have good antifouling properties. Boron-doped diamond electrodes are often touted as having high fouling resistance, but this has been shown to depend on the analyte, system conditions, and the surface of the electrode. The surface chemistry of boron-doped diamond electrodes can be altered to produce either H- or O-termination. There is some disagreement as to which type of termination has superior resistance to fouling, with some studies indicating O-termination (Güell et al. 2010, Shpilevaya and Foord 2014) and another suggesting H-termination (Brocenschi et al. 2014). Although H- or O-termination can have a significant impact on the fouling resistance of boron-doped diamond electrodes, few studies have investigated the use of oxidised carbon nanotubes or other oxidised carbon-based materials. Oxidation increases the number of oxygen functionalities on the electrode surface and thus hydrophilicity. It is debatable whether surface hydrophilicity or hydrophobicity increase fouling resistance, as it tends to depend on the analyte and fouling agents. Surface roughness has also been identified as a possible cause of electrode fouling (Zhuiykov and Kalantar-zadeh 2012, Xue et al. 2012, Shpilevaya and Foord 2014).

In addition to carbon-based materials, electrodes can also be modified with polymeric, nonpolymeric, and protein films that are not carbon allotropes to provide a physical barrier between fouling agents and the electrode surface. Such films, including Nafion (Razmi and Heidari 2009, Trouillon et al. 2009, Singh et al. 2011), thiols (Kuralay et al. 2011, McQuistan et al. 2014), and proteins (Picher et al. 2013, Qiu et al. 2013), also give rise to an increased background electrode capacitance and impedance, which is not favourable for the detection of trace analyte concentrations. Moreover, some self-assembled monolayers, including poly(ethylene glycol), can be self-oxidised and the oxidation products can be toxic for tissues upon implantation (Li et al. 2014). Therefore, alternatives to self-oxidising films and high capacitance/impedance films should be developed, such as the low impedance phenyl phosphorylcholine-modified electrode used by Gui et al. (2013). Although many of the polymeric film-modified electrodes discussed in this review were a single type of polymer with no additives, some studies that incorporated the PSS surfactant into the polymer showed good antifouling properties (Trouillon et al. 2009, Pirvu and Manole 2013, Sasso et al. 2013, Yang et al. 2013). Although the use of PSS is not necessary to provide protection from fouling, the incorporation of PSS or similar surfactants or compounds may improve the surface hydrophilicity and fouling resistance of a polymeric film.

Electrodes can also be modified with metallic nanoparticles or catalytic redox couples to improve the electrochemical response and fouling resistance. Several different types of nanoparticle were discussed in this review, including gold, nickel, palladium-nickel, and α-Fe_2O_3. To continue improving the antifouling properties of nanoparticles, new types of nanoparticles should be developed as well as improved attachment and functionalisation of the nanoparticles. Although two catalytic redox couples were specifically discussed, only the $Ni(OH)_2$/NiOOH redox couple was shown to impart antifouling properties (Safavi et al. 2009, Muna et al. 2014). Other metallic redox couples should be investigated for similar antifouling properties to $Ni(OH)_2$/NiOOH.

Nanoporous electrodes are resistant to fouling without the use of an electrode coating or film. The presence of nanoscale pores in the electrode structure prevents large fouling agents from reaching the inner surface of the electrode. Patel et al. (2013b) showed that only the presence of nanopores can effectively eliminate fouling from bovine serum albumin, as macroporous and hierarchical electrodes experienced fouling. Such a study, however, does not identify whether there is an upper or lower threshold pore size beyond which fouling occurs.

Electrochemical activation and electrolyte and flow systems do not involve the direct modification of the electrode but can also provide protection from fouling by removing adsorbed material or resisting its adsorption. Similar to the debate over whether H- or O-termination is superior for resisting fouling with boron-doped diamond electrodes, sometimes anodic pulses are superior for electrochemical activation, whereas, in other cases, cathodic pulses or a combination of anodic and cathodic pulses may be more appropriate. The choice could depend on the analyte, system conditions, and the type of electrode. Overall, this is indicative of the generally poor understanding of the pathways involved in electrode fouling and the mechanisms by which antifouling strategies are able to minimise or eliminate fouling. Therefore, research should be directed towards enhancing our understanding of fouling pathways and the specific mechanisms involved in resistance to fouling to develop more effective and versatile antifouling strategies.

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