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Review

Emerging graphene-based sensors for the detection of food adulterants and toxicants – A review

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ABSTRACT

The detection of food adulterants and toxicants can prevent a large variety of adverse health conditions for the global population. Through the process of rapid sensing enabled by deploying novel and robust sensors, the food industry can assist in the detection of adulterants and toxicants at trace levels. Sensor platforms which exploit graphene-based nanomaterials satisfy this requirement due to outstanding electrical, optical and thermal properties. The materials' facile conjugation with linkers and biomolecules along with the option for further enhancement using nanoparticles results in highly sensitive and selective sensing characteristics. This review highlights novel applications of graphene derivatives for detection covering three important approaches; optical, electrical (field-effect) and electrochemical sensing. Suitable graphene-based sensors for portable devices as point-of-need platforms are also presented. The future scope of these sensors is discussed to showcase how these emerging techniques will disrupt the food detection sector for years to come.

1. Introduction

1.1. Requirement of sensors for detection of adulterants and toxicants

Adulteration in food products is growing rapidly, impacting the safety and shelf life of consumer products. Validation and safety of food products 'fit for human consumption' is a priority for the food standard agencies (FSA) in the UK and the food safety and standards authority of India (FSSAI), alongside the other large food producing nations of the world. Compliance to the regulations is achieved by stringent monitoring during manufacture and random assessment of food products at the point of sale. Food adulteration is now widely spread in many products, including milk, meat, honey, fruit juices, vegetable oils, chips, jam, cereals, packaged foods and alcoholic beverages. The primary focus of any detection strategy relies on the categorization of the adulterant, the contamination level and the validation of this measurement. Laboratory based analytical techniques such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography-Mass Spectrometry (GC–MS), Fourier-Transform Infrared spectroscopy (FT-IR) and Nuclear Magnetic Resonance spectroscopy (NMR) are the industry standard for testing food products. Non-compliance, poor supply chain monitoring and contamination during the manufacturing processes can result in products reaching consumers adulterated. Advanced robust sensors that can be integrated with portable devices are now needed to detect adulteration at the point of sale, circumventing the laboratory-based analysis, reducing cost and decreasing the time required for product withdrawal (Cordella et al., 2002).

Along with sharing details of the latest sensing regimes applicable for food adulterants and toxicants, this review also considers the successes and obstacles of the adoption these technologies into the practical setting. It is the aspiration that this will lead future research into addressing some of issues raised. In Sections 2, 3 and 4 we discuss the graphene-based optical, electrical and electrochemical techniques along with their unique barriers for implementation into industry. Section 5 specifically highlights the methods for integrating these graphene-based strategies into portable devices, which will assist with the widespread proliferation of these strategies into real-world scenarios.

Many organic toxic compounds pose a risk to consumers and require detection in food stuffs to determine their prevalence. The sources of these adulterants range from poor farming practices, manufacturing,

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processing, packaging and environmental exposure during transit. Acrylamide and furans are examples of the compounds that are formed during food processing and have been highlighted recently due to the risk of health in consumers. Acrylamide has been linked to an increase in risk of developing cancer and is formed when plant-based foods are heated therefore occurring in foods that have been baked, fried or roasted such as potato products, cereal grains and coffee. Furans, which are possibly carcinogenic and found commonly in canned and jarred foods are formed during any thermal treatment of food stuffs (Stadler, 2019).

Inorganic compounds also pose a threat to food production due to their ubiquitous prevalence and persistence. Toxic metals like arsenic, lead, chromium, mercury and cadmium pose a particular threat even at low concentrations. Lead is also still having a huge impact on human health; currently illustrated by the Flint, Michigan exposure, which has clear and definitive sources (Hanna-Attisha et al., 2016). Human bone stores lead indefinitely and this can be the root cause of associated diseases. Without a direct biopsy from the bone the amount of lead within the human system has to be estimated upon the current blood lead levels and the total exposure time (Bellinger, 2008). Lead can enter the body via the airborne tract where it is absorbed through lung tissue, or primarily through the digestive tract where exposure usually occurs through drinking water.

Inorganic arsenic, which occurs naturally in the soil, is now prevalent in drinking water throughout the Asian sub-continent, its presence is mostly of the form arsenate (V) but has a number of oxidation states also forming sulphides and metal arsenides. WHO recommends levels no greater than 10 μg/L (WHO, 2020). In this area demands to feed an ever-increasing population relies on the cultivation of rice on a vast scale, which forms a primary food source in this area. The combination of relatively high levels of arsenic in rice along with further exposure due to industrial by-products is causing widespread arsenic poisoning (Meharg, 2004; Heitkemper et al., 2001).

Industrial processes such as leather tanning, metal plating and textile processes often discharge waste quantities of chromium (Cr) into waterways where the toxic speciation of this metal can easily enter the food chain. Although Cr (III) is an essential element for the correct functioning of the human body, Cr (VI) is noted to be severely toxic and classified as a group 1 human carcinogen by the IARC (Tomatis et al., 1991).

In aqueous environments, the mercury ion (Hg^{2+}) species is converted from the volatile Hg (0) via atmospheric oxidation/reduction reactions, cycling repeatedly until ingested by fish, mammals and humans. Elemental mercury enters the human food chain and leads to kidney abnormalities and neurological impairment. Further toxic speciation includes the production of methylmercury $[CH_3Hg]^+$ from inorganic mercury, traces of which have been identified in shellfish from polluted waters. Exposure to methylmercury results in damage to the nervous system, infantile developmental abnormalities and cerebral palsy (Counter & Buchanan, 2004).

The processing and handling of fruit juices and soft drinks using cadmium (Cd) plated vessels is one way this material directly enters the food chain (Bansal et al., 2017). Cadmium can be biologically active for up to 30 years so very low doses can accumulate and present as detrimental symptoms within a lifetime, specifically damaging the kidneys (Arain et al., 2015).

Pest control chemicals are commonly used to control the insects in crops, vegetables and fruits. One commonly used pesticide, fenitrothiron is a nitroaromatic compound, which is partially soluble in water. The detection of fernitrothiron is important in order to prevent adverse health effects as this chemical degrades into the toxic compounds fenitrooxon and 3–methyl–4–nitrophenol, which affects food and water sources (Kant, 2019). Veterinary growth promoter drugs create serious impact on human health due to accumulation, triggering conditions like tremors and nausea. Clenbuterol is one among these muscles inducing veterinary drugs, which has been banned in many countries. Yet, it is used illegally to promote high muscle mass specifically in calves and horses. This potential risk creates a mandatory condition for detection of clenbuterol at early stages in food products (Cheng et al., 2020).

Analytic sensing techniques detect transitions in chemical or biological events and often represent these as a change in electrical response. Biological sensors or biosensors are platforms that transduce binding events by immobilizing receptors such as antibodies and aptamers, analytes interact with these receptors resulting in a change in signal output. Biosensors express good sensitivity and specificity and can be widely used for the monitoring of packaged food products assessing the freshness of items such as fruits, vegetables, fish and meat products (Mustafa & Andreescu, 2018).

Integrating nanomaterials (NMs) with biosensors can enhance the sensitivity and specificity for target analytes which are fundamental sensing characteristics. Optical sensing strategies suitable for biosensing are surface-plasmon resonance (SPR), surface-enhanced Raman scattering (SERS) and fluorescence-based techniques. The most widely explored optical sensors are DNA sensors and immunosensors conjugated with nanoparticles (NPs). DNAzyme probes are also used for real-time monitoring of food pathogens using fluorescence quenching to minimize food-borne illnesses. Fluorescence quenching is useful for the detection of *E. coli* in solid and liquid food samples without relying on the lysis process, reducing processing time and associated costs (Liu et al., 2018a). Nanobiosensors show promising results in food microbiology for the detection of pathogens, in particular, biosensors based on carbon NMs have gained much attention due to their rapid detection mechanism and cost-effectiveness (Singh et al., 2017).

Electrochemical sensors (EcS), particularly screen-printed electrodes (SPE) based on carbon NMs, act as robust tools for high sensitivity with good detection reproducibility. Carbon NMs can be integrated with metal oxide NPs made from gold, iron oxide and zinc using electrochemical and immunoassay techniques. Calorimetric and fluorometric sensors have been developed using carbon NMs for detection of pesticides containing carbamate and organophosphates compounds. Quartz crystal microbalance (QCM) immunosensors are also important tools for low cost and label-free measurements. Magnetic NMs are widely used as amplifiers in QCM immunosensors for the rapid and sensitive screening of food borne pathogens (Kumar et al., 2012). Categories of NM-based sensors were explored for the detection of bacterial pathogens in meat products by (Stephen Inbaraj & Chen, 2016). Polymerase chain reaction (PCR), has good merits in terms of specificity, rapidity and accuracy for the detection of microbial pathogens however, difficulties in quantification, generation of false-positives during detection and sample contamination currently limits the extensive usage of the PCR technique (Palchetti & Mascini, 2008).

1.2. Robust graphene-based materials as optical, electrical, electrochemical sensors

Three of the primary detection regimes for biosensors are optical, electrical and electrochemical and are discussed in detail in this section. Table 1 gives an overview of these three sensing strategies for the detection of OTA in food products, detailing the sensing time, reagents and pre/post processing steps for real food applications. More details on these sensing strategies can be found in Sections 2.1, 3.1 and 4.1 respectively. Despite the importance of food sample pre/post processing for the practical implementation of sensing regimes a detailed discussion on these procedures is beyond the scope of this review.

Graphene exhibits an electron band structure with high carrier mobility promoting graphene as an optical sensor. The optical properties of graphene are due to the regular distribution of dirac electrons. Monolayers of graphene can absorb light from visible range and have a resonant optical response to photons from ultraviolet to infrared. These properties emerge from interband and intraband energy band transitions, thus, graphene is a suitable material for near-infrared band photo responses. Despite the low absorbance value of 2.3% (visible to terahertz

Table 1
Comparative overview on optical, electrical and electrochemical techniques for the detection of OTA target in food products.

Technique	Food product		Sensing Details				Reference
	Sample	Pre/Post Processing	Activation	Bioreceptor Immobilisation	Surface Passivation	Readout	
Fluorescence sensing	Red wine	Samples filtered to remove sediments and diluted with buffer solution	OTA targets added to OTA aptamers with FAM fluorophore (300 nM) in NEBuffer 2 for 15 min. GO (10 μg/mL) added for 15 min	n/a	n/a	$RecJ_f$ (0.06 U/μL) added and fluorescence intensity recorded after 90 min	Zhao et al., 2020
GFET – Liquid gating	Red wine	Samples centrifuged to remove large particles prior to spiking	GFET treated with PBASE in DMF solution (1 mM) for 6 h	Soaking of OTA aptamers in PBS solution (5 μM) for 4 h	Ethanolamine in PBS solution (100 mM) for 1 h	OTA target added and binding process completed within 5 min	Nekrasov et al., 2019
Graphene oxide electrochemical sensor - DPV	Ground wheat	Samples underwent milling, shaking and filtering.	SPCE treated with Nafion (1.0%, v/v) under infrared for 20 min	Drop casting of Thionine-labelled OTA aptamers (10 μg/mL)	n/a	Signal monitored after OTA target incubation for 90 min	Sun et al., 2017

broad band), graphene's optical properties can be enhanced using other NMs. Graphene is also suitable for the detection of both chemical and biological compounds, overcoming the inherent lack of specificity by using graphene as optical sensors in conjunction with other techniques for example, SPR, SERS and fluorescence spectroscopy (Li et al., 2019a).

Using 3D printing technology printed electrodes electrochemically adapted for food analysis can be manufactured at scale. Nasir et al. developed graphene-based electrodes using the fused deposition modelling (FDM) technique possessing high catalytic activity and absorption ability for the detection of specific analytes in food products (Zafir Mohamad Nasir et al., 2020). Graphene ink formulation is a developing field for rapid fabrication of electrodes using aerosol jet printing (AJP) technique, printing at a 5 mm/s print rate (Parate et al., 2020). One of the main challenges in developing electrochemical based graphene sensors is a compatible potentiostat and on-chip integration (Bobrinetskiy & Knezevic, 2018).

Table 2
Overview of graphene-based optical, electrical and electrochemical sensors with LOD and dynamic range corresponding to target molecule.

Type of Material	Target	LOD	Dynamic Range	Technique
Graphene quantum dot, Gold Nanoparticles	Cyanide (Plant tissue)	0.52 μM	0–500 μM	Fluorescence (Wang et al., 2015)
Graphene, Cy3 aptamer Fluor 488 aptamer	Zearalenone, ochratoxin A (Mycotoxin in food products)	1.797, 1.484 ng/mL	1–500 ng/mL	Fluorescence (Wang et al., 2020a)
Graphene oxide, FITC conjugated antibody	Cry2Ab (Transgenic Plants)	0.546 ng/mL	12.5–0.78 ng/mL	Fluorescence (Smitha et al., 2020)
Graphene oxide, carboxyfluorescein labelled aptamer	Aflatoxin M1 (Milk powder)	0.05 μg/kg	0.2–10 μg/kg	Fluorescence (Guo et al., 2019)
Reduced graphene oxide, Ta_2O_5 nanoparticles	Fenitrothion (cereals, fruits, vegetable)	38 nM	0.25–4 μM	SPR (Kant, 2019)
Graphene protected Cu	HT-2 mycotoxin (Oats, barley, wheat)	0.5 fg/mL	1 pg/mL	SPR (Wu et al., 2019)
Chitosan-GO-Cadmium sulfide QDs	Cobalt ion	0.1 ppm	0.1–100 ppm	SPR (Omar et al., 2019)
Graphene oxide, Gold Nanoparticles	Thiram (Fruits and vegetables)	1 μM	1 μM – 1 mM	SERS (Lee & Kim, 2019)
Graphene oxide, Gold Nanoparticles	Clenbuterol (animal-origin food)	1 ng/g	1–100 ng/g	SERS (Cheng et al., 2020)
Graphene, Gold Nanorods	Azinphos-methyl, carbaryl, phosmet (Pesticide)	5,5,9 ppm	0.01–100 ppm	SERS (Nguyen et al., 2014)
Graphene, Aptamer	Adenosine triphosphate	0.5 pM	0.5 pM–50 μM	FET (Xu et al., 2019)
Graphene, Aptamer (Cereal grain, dried fruits, wine)	Ochratoxin A	4 pg/mL	10 pg/mL–4 ng/mL	FET (Nekrasov et al., 2019)
Graphene, Aptamer	Mercury Ion (Hg^{2+})	40 pM	100 pM – 100 nM	FET (Tu et al., 2018)
Graphene, Antibody	Botulinum neurotoxin	1 μM	n/a	FET (Kim et al., 2017)
Graphene, ssDNA (dsDNA)	Bisphenol A	1 μg/mL (10 ng/mL)	1 μg/mL (10 ng/mL) – 100 μg/mL	FET (Liu et al., 2018a)
Graphene, DNA	Lead Ion (Pb^{2+})	20 nM	n/a	FET (Chee et al., 2017)
Reduced graphene Oxide, Silver-palladium alloy nanoparticles	Ractopamine, Salbutamol, Clenbuterol (β-adrenergic agonists)	1.52, 1.44, 1.38 pg/mL	0.01–100 ng/mL	CV (Wang et al., 2013a)
Graphene-gold NPs-Hemoglobin hybrids	NO_2^-	0.01 μM	0.05 to 1000 μM	Amperometry (Jiang et al., 2014)
Graphene/phosphotungstic acid hybrid	SY and TT	0.5 and 30 ng/mL	1.0–300.0 μg/L and 60.0 μg/L – 1.5 mg/L	DPV (Gan et al., 2012)
rGO/MoS2/PANI/AuNPs/Aptamer	Aflatoxin B1	0.002 fg/mL	0.01 fg/mL – 1.0 fg/mL	DPV (Geleta et al., 2018)
Graphene/Fe3O4 and AChE	Chlorpyrifos	20 pg/mL	0.05 μg/L – 100 μg/L	DPV (Wang et al., 2016)
Graphene, Aptamer (Coffee, cocoa, beer, wine)	Ochratoxin A	5.6 pg/mL	0.01–50 ng/mL	DPV (Sun et al., 2017)
Graphene, Fe_3O_4, AuNPs, Aptamer	Streptomycin (Antibiotic)	0.028 ng/mL	0.05–200 ng/mL	DPV (Yin et al., 2017)
Graphene, molecularly imprinted polymers (MIP)	Imidacloprid (Insecticide)	0.10 μM	0.5–15 μM	CV, LSV (Zhang et al., 2017)

Abbreviations: FITC- Fluorescein isothiocyanate, Ta2O5 - Tantalum pentoxide, SPR- Surface plasmon resonance, Cu- copper, SERS- Surface-enhanced Raman spectroscopy, FET- field-effect transistor, CV- cyclic voltammetry, SS- Sunset yellow, TT- Tartrazine, AChE- Acetylcholinesterase, DPV- Differential pulse voltammetry, Fe3O4 - Iron oxide, AuNPs- Gold nanoparticles, LSV- Linear sweep voltammetry.

A primary motivator for using graphene in biosensing platforms is the simplicity in chemical functionalization (Novoselov et al., 2012). A variety of bioreceptors can be added to the surface of graphene which bind selectively to target analytes; aptamers (Xu et al., 2019), antibodies (Kim et al., 2017) and DNA (Liu et al., 2018b) are some examples of the bioreceptors used to functionalize the surface of graphene field effect transistors (GFETs) biosensors. Bi-functional molecules such as 1-pyrenebutyric acid *N*-hydroxysuccinimide ester (PBASE) can be used to facilitate the non-covalent functionalization of graphene at the pyrene end and the immobilization of bioreceptors at the *N*-hydroxysuccinimide ester end (Chen et al., 2001). Covalent binding strategies, which introduce defects to the graphene lattice, can encourage the absorption of molecules onto the graphene surface thus reducing the specificity of the sensing device and so are avoided (Kim et al., 2017, Ohno et al., 2010).

Table 2 presents an overview of graphene-based sensors explored using optical (Fluorescence, SPR, SERS); electrical (FET); and electrochemical (CV, DPV, LSV) techniques with limit of detection (LOD) and dynamic range corresponding to the target molecule (prevalence in various food products). In addition to the discussion on the current state of these techniques this review also aims to highlight the obstacles that slow the adoption of these technologies in practical settings, thus inspiring the research community to investigate the necessary solutions.

2. Graphene optical sensors

2.1. Applications of graphene-based optical sensors in food adulterants and toxicants detection

2.1.1. Fluorescence spectroscopy

Fluorescence detection of biomolecules and food contaminants requires a fluorescent active material or dye to be conjugated with the target analyte. Graphene quantum dots (GQDs), exhibit both sp^2 and sp^3 hybridized carbon atoms, and a size-dependent optical bandgap. Additionally, their inherent 2D structure enables strong π-π interactions during conjugation with target molecules. The addition of functional groups can induce energy transitions leading into a change in fluorescence peak wavelength, fine tuning the GQDs to optimize a desired fluorescence, from lower to a higher wavelength. Wang et al explored the two-photon excitation (TPE) property of GQDs with gold nanoparticles (AuNPs) for detection of cyanide (CN^-) in plant tissues. CN^- possesses a great threat as a toxic substance and gets exposed to mammals through the consumption of food products and plants. This creates a requirement to assess the levels of cyanide in plant tissues. GQDs gained popularity for biosensing and bioimaging applications due to their excellent photostability and tunable fluorescence properties. AuNPs were functionalized with peptide molecules and GQDs were decorated on the surface of AuNPs. The interference of cyanide etches AuNPs-peptide to disassociate with GQDs. The fluorescence of GQDs is quenched by AuNPs possibly by fluorescence resonance energy transfer (FRET) process. The LOD of cyanide is found to be 0.52 μM. The selectivity of sensors was analyzed using the influence of other anions such as SCN^-, H_2S, Br^-, Cl^-, NO_2^-, SO_4^{2-} etc. which did not influence the response during detection of cyanide. It is also observed that pretreatment of plant tissues such as washing and soaking for a certain period could remove the cyanide traces. Thus, AuNPs-peptide with GQDs could be a promising combination for sensing and imaging CN^- from plant tissues. This paves way for the development of two-photon fluorescent GQDs nanomaterials for potential food safety applications (Wang et al., 2015).

Graphene Oxide (GO) functionalized with aptamers (ssDNA) can be used to detect agricultural pollutants such as Hg^{2+} Cd^{2+} and Co^{2+} by forming a hairpin structure on GO quenching the fluorescent marker (Zheng & Wu, 2017). Furthermore, GO can also be conjugated with DNA and G-quadruplex (ssDNA) and used as fluorescence biosensors for detection of food contaminants. GO exhibits good adsorption capacity of DNA acting as a fluorescent acceptor in the FRET technique. Wang et al. demonstrated this technique by using a combination of GO with aptamers for monitoring toxins of biofilms produced in food products. The LOD was reported as 1.797 ng/ml and 1.484 ng/ml for ZEN and OTA respectively. GO plays an important role as a switch and triggers fluorescence switch-on state with the presence of target molecules. The change in fluorescence intensity is significant with and without the presence of dual targets ZEN and OTA. The constructed GO-aptamer platform offers convenient detection for mycotoxins in food products using the fluorescence technique. This report indicates that portable devices using the GO-aptamer combination could be developed for multiplexed detection at low cost (Wang et al., 2020b). Zhao's groups demonstrated a fluorescence-based aptasensor based mechanism for detection of OTA using GO and $RecJ_f$ exonuclease. Hydrolysis of OTA-aptamer by $RecJ_f$ indicates the enhancement of the fluorescence signal at 90 mins. LOD is found to be 0.07 ng/mL with a dynamic range of detection (2, 4, 6 and 20 ng/mL). OTA was further spiked into red wine samples at different concentrations to analyze the sensor performance (Zhao et al., 2020).

Transgenic plants are at risk of contamination due to the presence of endotoxins such as pesticidal crystal proteins (CRY). GO conjugated with antibodies is used for the detection of insecticidal protein Cry2Ab expressed in transgenic cotton. GO and Fluorescein isothiocyanate (FITC) conjugate are used as energy acceptor and donor candidates and bridged with (the target) analyte protein. Fluorescence quenching linked immunosorbent assay was used to determine a series of Cry2Ab concentrations from 0.39 to 2.5 ng/mL as shown in Fig. 1 (A) (Smitha et al., 2020).

Detection of adulterants and toxic elements in milk is becoming an increasing concern among consumers. Aptasensors on a robust GO thin film emerges as a suitable platform for hydrophobic stacking interactions between nucleobases and GO. GO with aptamers was explored for amplified fluorescence detection of Aflatoxin M1 (AFM1), toxic mycotoxins found in dairy products like milk. A change in fluorescence signal intensity indicates the signal amplification caused by AFM1/aptamer complex. The aptamers are released from the surface of GO to conjugate with AFM1. The aptamers' sequence was modified with fluorescent material FAM (carboxyfluorescein) before conjugating with target material. The fluorescence emission was recorded in the range of 510 to 630 nm. Different mycotoxins such as AFB1, OTA, ZEN and α-zearalenin (α-ZOL) were analyzed to test for specificity at the same concentration of 4 ng/ml. The detected range of AFM1 was 0.2 to 10 μg/kg with a LOD of 0.05 μg/kg showing promising results for low-cost and rapid sensing of dairy products. This example also showcases how these novel platforms can be tuned to detect other adulterants and toxicants by changing the sequences of the immobilized aptamers, Fig. 1 (B) (Guo et al., 2019). GO acts as both fluorophore and quencher opening up a new opportunity, which enables graphene-based sensors for agriculture and food safety applications, Fig. 1 (C) (Zheng & Wu, 2017).

2.1.2. Surface plasmon resonance (SPR)

SPR has become an established tool for biosensing, such as DNA-protein, protein–protein, protein-drug interactions, electrochemical analysis and molecular detection. It is also an established technique for label-free sensing of bio-molecular species, including time-dependent reaction analysis (Schasfoort & Tudos, 2008). Measurement of biomolecular interactions on the surface of gold thin films has emerged as one of the leading techniques for fast in-situ detection of a wide range of biological targets, critical to medical diagnostics and environmental monitoring (Law et al., 2009). Graphene has proved to be an appropriate dielectric top layer for SPR sensors. The deposition of graphene layers over gold film can improve the sensitivity of the device. Thus, graphene can be integrated into biosensor chips, which enables the sensor to be highly sensitive to small alterations in the refractive index of a medium, Fig. 1 (D) (Salah et al., 2014). Graphene-based SPR sensor chips were used for rapid detection of cobalt ion as low as 0.1 ppm with dynamic

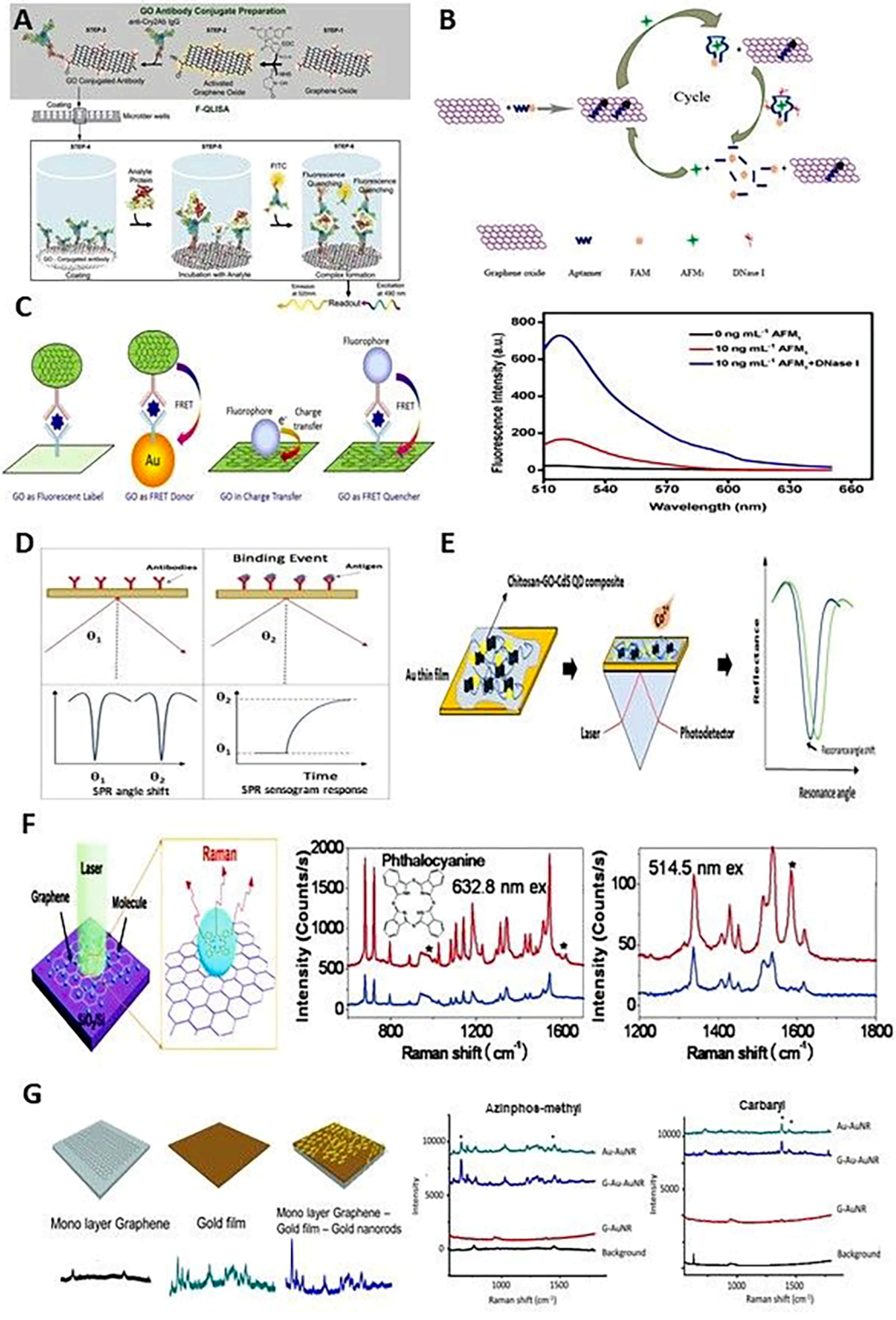

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Fig. 1. Overview of graphene-based optical sensing techniques. (A) The development of Graphene-oxide-based fluorescent quenching-linked immunosorbent assays (F-QLISA) for the detection of Cry2Ab protein. Reprinted with permission from ACS publication (Smitha et al., 2020). (B) Schematic of graphene oxide-based aptasensor for the detection of aflatoxin M_1 (AFM_1) in milk powder, FAM: carboxyfluorescein. The bottom panel shows the fluorescence emission spectra in the absence of AFM_1 and in the presence of 10 ng/mL AFM_1, and where the fluorescent intensity is enhanced by the addition of DNase I to AFM_1 (Guo et al., 2019). (C) Schematic of graphene oxide-based sensor design showing GO as a fluorescent label, GO as a FRET donor and quenching mechanism by electron charge transfer and the FRET process. Reprinted with permission from Wiley (Zheng & Wu, 2017). (D) Schematic view of the SPR immunoassay technique. For a functionalized SPR sensor layer on top of a conventional glass prism/gold plasmonic system, a binding event occurs on the glass prism/gold plasmonic system, revealing an SPR angle shift from θ_1 to θ_2 and the SPR sensorgram response in the time domain changing following the binding event (adapted from Salah et al., 2014). (E) Chitosan-GO-Cadmium sulfide QDs composite thin film for detection of cobalt ion using SPR technique. The increase in the cobalt ion concentration induces the resonance angle shift to the right (Omar et al., 2019). (F) Schematic of molecules on a graphene surface on a SiO_2/Si substrate for Raman enhancement, Raman signals of phthalocyanine deposited 2 Å on SiO_2/Si substrate (blue line) and on graphene (red line) at 632.8 nm excitation. The intensity of Raman signals at 632.8 nm excitation is larger than 514.5 nm, indicating the adsorption of molecules at 632.8 nm is stronger than at 514.5 nm. Adapted with permission from ACS publication (Ling et al., 2010). (G) Illustration of comparative SERS signals for a monolayer of graphene, gold film and a monolayer graphene-gold film-gold nanorods combination showing the Raman spectra of 100 ppm of azinphos-methyl and carbaryl on different substrates. An asterisk (*) shows the characteristic band of corresponding pesticides. Adapted with permission from ACS publication (Nguyen et al., 2014). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

range 0.1 to 100 ppm. The possible binding affinity of cobalt ion on sensor layer was induced by electrostatic force between graphene oxide and cadmium sulfide QDs, Fig. 1 (E) (Omar et al., 2019).

In graphene-based SPR immunosensors, the sensitivity can be optimized by carefully tuning the number of graphene layers relative to the thickness of metallic layer, the greater the number of layers, the greater the SPR imaginary dielectric constant (Maharana et al., 2013; Saifur Rahman et al., 2017). In addition, a GO-based SPR configuration was presented by Chiu et al. as a sensing platform, with a high covalent binding affinity for protein molecules, which lead to a LOD of 100 pg/ml for BSA detection. The sensitivity and selectivity were improved by carboylating the GO surface. The carboxyl-GO based SPR sensor provided high affinity and stronger binding of peptides, which is very significant for a non-immunological label-free mechanism (Chiu & Huang, 2014). Chiu et al achieved a LOD of 1.15 pg/mL for the detection of human chorionic gonadotropin in clinical serum samples (Chiu et al., 2019).

2.1.3. Localized surface plasmon resonance (LSPR)

LSPR is confined to NPs when the free electrons participate in the collective oscillation. With NPs the surface charge to volume range is much greater and so electrical fields near the NPs are strongly localized and can be greatly enhanced. This is why LSPR is applicable in molecular detection, i.e. bio- and chemical sensors, refractive index sensors and gas sensors. For this enhancement, the surface may incorporate metallic NPs as a two-dimensional array, in a similar way that sensors are designed for SERS. Again, the enhancement is a function of the array configuration, such as how closely spaced the NP array is. The surface may also be nanostructured to incorporate arrays of metallic features, such as split rings. As with SPR the metallic materials used are silver (Ag) or gold (Au).

LSPR sensors can also incorporate graphene to change the plasmonic response. As with SPR, the graphene layer is on top of the plasmonic layer. How does graphene change the localized plasmonic response? This has been systematically modelled by El Barghouti (El barghouti et al., 2018) who showed that sensitivity was optimized for a 2 nm graphene layer.

The effect of graphene on the LSPR of metal NPs was explored by Nan et al (Nan et al., 2018) who studied two transparent graphene-metal NP hybrid schemes. They investigated Au NPs covered by graphene layers and Au NPs encapsulated by graphene layers. In each case, the electron transfer from Au NPs to graphene, caused by the direct contact between the two, strongly tuned the resonant frequency. This formed the basis of their model discussed in their work. For this study 24 nm Au NPs were fabricated on a 5 nm Au film on glass, and the graphene films were transferred using a standard PMMA technique. 0, 1, 2, 3 and 4 layers of graphene were studied. The Au NPs caused redshifting in the plasmon resonant frequency which remained constant with the coverage or encapsulation of additional graphene layers.

2.1.4. Surface-enhanced raman spectroscopy (SERS)

Surface enhanced Raman spectroscopy (SERS) is an important spectroscopy technique that deals with detection at trace levels with high sensitivity and specificity. Thus, the SERS technique is widely explored in the analysis of food contaminations and several applications related to analytical chemistry for specifically identifying contaminants in food products. SERS substrates are the important platform to enhance the Raman signal during detection of target materials. SERS substrate materials are fine-tuned to optimize the required plasmonic characteristics. This technique requires a substrate that exhibits fine precision at the atomic scale and robust nature. Graphene can be easily conjugated with metal NPs to achieve a good resolution during SERS sensing. Graphene can be used as an excellent substrate for enhancing Raman signals. A comparative analysis showed the signals of Phthalocyanine on graphene are much stronger than conventional SiO_2/Si substrate, Fig. 1 (F) (Ling et al., 2010). Compared to SiO_2/Si substrate, graphene exhibit both resonant and chemical enhancement. Thus, graphene is suitable for enhancing Raman signals compared to metals.

In one example, Nguyen et al. fabricated a combination of graphene and gold nanorods SERS substrates for the detection of insecticides such as azinphos-methyl and phosmet; pesticide like carbaryl. The LOD was found to be 5 ppm for azinphos-methyl, carbaryl and 9 ppm for phosmet. Gold nanorods were cast on graphene monolayer and a gold film with 40 nm thickness was deposited on the substrate. Graphene plays an important role in SERS enhancement along with gold nanostructures like nanorods and films. The reports claim that the SERS enhancement can happen due to the contribution of thermal conductivity of graphene due to exposure and influence of laser power, Fig. 1 (G) (Nguyen et al., 2014). Schedin and group identified that gold nanorods significantly improves the Raman signals with reduced graphene oxide. They explored the SERS technique using graphene patterned with gold nanodisk on SiO_2/Si substrate and observed the G and 2D bands of graphene were enhanced at 633 nm (Schedin et al., 2010). The number of graphene layers are directly related to Raman signal strength with a few-layers of graphene the enhancement factor increases up to a maximum of 12 with the signal becoming weaker in case of additional layers. Thus, monolayer graphene is found to be the best signal enhancer for SERS technique. The chemical enhancement also plays a vital role and it depends on surface properties and geometry of the molecules.

2.2. Challenges to graphene-based optical sensors for detecting food adulterants and toxicants

Graphene oxide can suffer from defects in the lattice structure due to the oxidation process interfering with the heterogeneous electron transfer. Although certain defects in GO are useful for conjugation of molecules and linkers, these defects may influence the optical sensing properties of target molecules. The graphene derivatives exhibit a combination of broadband transparency and tunable electronic

conductivity. Before the functionalization of GO, the defects have to be validated to achieve proper conjugation with smaller molecules like enzymes and peptides, this is an important factor to determine the quenching property of GO (Reina et al., 2017). Graphene-based optical sensors always require suitable protection to prevent EM and optical interference. Pristine monolayer graphene is always a high priority for sensing adulterants and toxicants at trace levels requiring techniques such as chemical vapour deposition (CVD) to obtain graphene in a high-yield cost effective manner.

The practical difficulties for utilizing SPR technique includes the aggregation of analytes within samples and the pH induced precipitation interfering with the optical sensitivity impacting the photo-induced current, which diminishes the signal output (Wu et al., 2010). SPR is meeting the challenge of detection by modification of the sensor chip to include an array of Ag or Au NPs to enhance the localized electric field, known as LSPR. Additionally, graphene enhanced LSPR devices have been modelled, fabricated and characterized, but there is limited published data on implementation in bio-sensing. Graphene has also been incorporated into SERS, a 2020 paper by Valeš (Valeš et al., 2020) on Graphene-enhanced Raman scattering (GERS) studied mono and bilayer pristine graphene partially hydrogenated to enhance the Raman signal whilst improving the quench photoluminescence simultaneously. This work highlights the change of Raman signal bands of rhodamine 6 G (R6G) when using hydrogenated and pristine graphene. It was proposed that GERS and electrochemical sensing could be combined which would further develop the applications of hydrogenated graphene in future sensor applications. Moreover, other functional species could be used to replace hydrogen thus creating the next wave of novel electrochemical sensing platforms (Valeš et al., 2020).

3. Graphene field effect transistor sensors

3.1. Mechanism of graphene field effect transistors sensors

Graphene field effect transistors (GFET) are semiconductor devices that use a graphene channel between metallic source and drain electrodes. The current (I_{SD}) in the channel induced by a potential difference (V_{SD}) between the source and drain electrodes is modulated by the application of an applied electric field stimulated by a voltage (V_G) at the gate terminal (Tran & Mulchandani, 2016). Transfer curve characteristics for GFETs are obtained during gated voltage sweep measurements (I_{SD}-V_G), where V_{SD} is held constant whilst V_G is swept from $-V_{GMax}$ to V_{GMax} to obtain the transfer curve characteristics for the device (Yang et al., 2012). Charge neutral points, corresponding to the points of minimum charge carriers and conductivity in the channels are referred to as Dirac points (Reddy et al., 2011; Tran & Mulchandani, 2016).

Gating of the channel is achieved in one of two ways as demonstrated by Fig. 2 (A). Firstly, back-gated GFETs position the graphene channel on the surface of a SiO_2/Si stack, the SiO_2 layer acts as an insulating layer which facilitates the field effect operation of the GFET when charge carriers are induced by the highly degenerate Si layer acting as the gate terminal (Fu et al., 2017; Li et al., 2017). Liquid-gated GFETs closely resemble the configuration of traditional Si-based Ion Sensitive Field Effect Transistors (ISFETs) and are used for detecting analytes within solutions. In this design graphene sits directly on the surface of a Si substrate and an electrolyte is contained on the surface of the graphene by the use of microfluidic systems (Fu et al., 2017) using insulating materials such as silicone (Matsumoto et al., 2014, Ohno et al., 2015). A reference electrode is then immersed within the electrolyte. When a voltage is applied across the reference and source electrodes, ions in the buffer solution are attracted to the electrodes and counterions

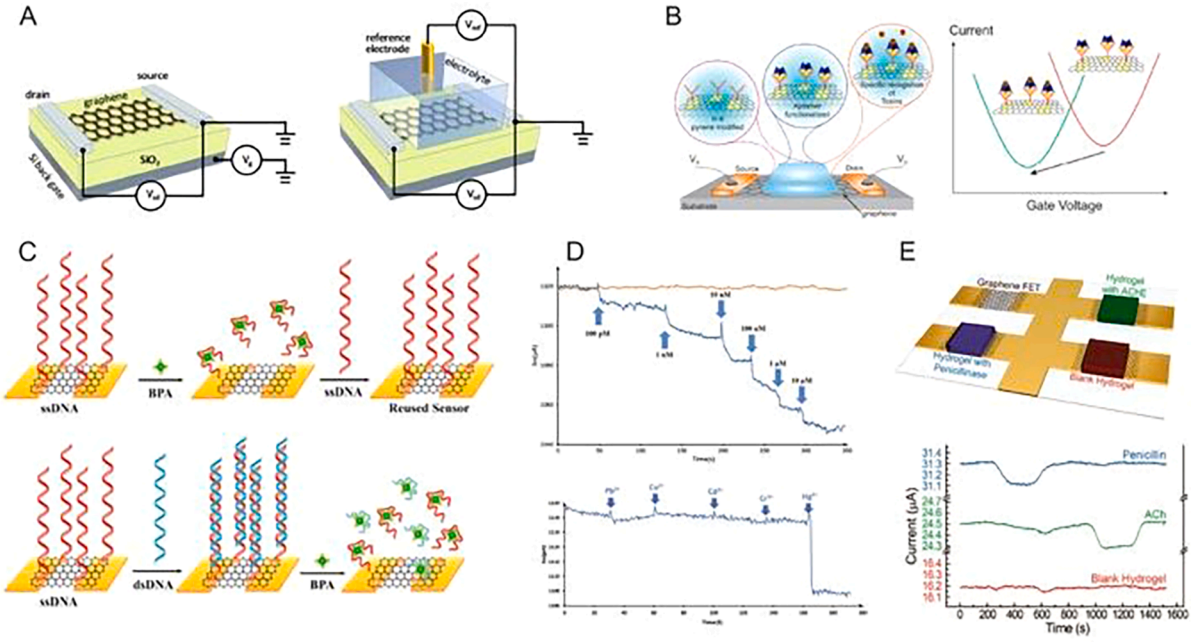

Fig. 2. Overview of graphene-based electrical sensing techniques. (A) Experimental setup for a typical I_{SD}-V_G measurement for left panel: Back-gated and right panel: Liquid-gated GFET devices. Adapted with permission from (Fu et al., 2017) Copyright (2017) John Wiley and Sons. (B) Left panel: Sensing process for GFET aptasensor for Ochratoxin A. Right panel: Example shift in I_{SD}-V_G caused during detection of toxic material (Nekrasov et al., 2019). (C) Reusable BPA sensing GFET device using immobilised upper panel: sDNA and lower panel: dsDNA that release from Au-NP decorated graphene surface during detection events. Reprinted with permission from (S. Liu et al 2018) Copyright (2018) American Chemical Society. (D) Upper panel: GFET device response with increasing concentration of Hg^{2+} ion, from 100 pM to 10 μM, against control target. Lower panel: Selectivity of device for Hg^{2+} over competing metal ions (Pb^{2+} Cu^{2+}, Cr^{3+}, Cd^{2+}) (Tu et al., 2018). (E) Upper panel: GFET devices with penicillinase (blue), acetylcholinesterase (green) and blank (red) bioreceptors encapsulated into hydrogels patterned over graphene channels. Lower panel: Simultaneous and selective sensing response when penicillin (blue), acetylcholine chloride (green) and control (red) analytes introduced onto the GFETs via the shared microfluidic channel. Adapted with permission from (Bay et al., 2019) Copyright (2019) American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

are attracted to these surface charges. This forms an electrical double layer on the graphene surface which acts as an insulating gate layer (Ohno et al., 2015), consequently allowing the field effect operation in this format.

Conducting measurements with a dry graphene surface is required for back-gated GFETs, simplifying the fabrication process, as an electrolyte well and insulation for metallic electrodes are no longer required (Kakatkar et al., 2015). This sensing scheme also facilitates vapour detection and simplifies the detection of targets within solutions of varying compositions (Green & Norton, 2015). An advantage of the liquid-gating mechanism for GFETs is the lower sweep voltage required to observe ambipolar behavior, seen between ±0.1 V against the requirement to sweep V_G between at least ±20 V for equivalent back-gated devices (Tran & Mulchandani, 2016). One important consideration that limits the sensitivity of liquid-gated devices is the Debye length, which describes the maximum distance that charge carriers in the graphene channel are influenced by the target analytes in the detection medium (Ohno et al., 2010).

3.2. Applications in food adulterants and toxicants detection

Aptamers are single stranded DNA molecules that are synthesized in vitro (Ohno et al., 2010; Matsumoto et al., 2014). They are less expensive to produce than antibodies, stable and crucially are small enough in length (~3 nm) to be within the Debye length (~5 nm at room temperature in 5–10 mM buffer solutions) allowing electrical detection (Ohno et al., 2010). Xu and colleagues used aptamer functionalized graphene foam field effect transistors (GF-FETs) to enable the label-free detection of ATP. As ATP is the primary energy molecule of cells, it can be used as an indicator to correlate with biomass and therefore contamination levels in food stuff (Xu et al., 2019).

Nekrasov et al. demonstrated the first aptamer functionalized GFET biosensor for the detection of OTA, Fig. 2 (B) with a LOD of 4 pg/mL (Nekrasov et al., 2019). As one of the most common foodborne toxins, OTA is a mycotoxin found in a variety of different foodstuffs, impacts the kidneys and is resistant to thermal treatment. They deployed a liquid-gated GFET design, based on CVD graphene, where aptamers were immobilized onto the surface of graphene via PBASE. Nekrasov showed that the device was not only specific to OTA, by testing the resistance response against a pristine sensing surface and observing no significant change at a concentration of 20 pM, but also that these devices were selective to OTA over another toxin, ZEN by confirming that the response was 5 and 7 times lower than that of OTA for concentrations at 60 nM and 600 nM respectively. This group then validated their sensors by testing the response against spiked wine samples and observed a good agreement between the spiked and detected concentrations of OTA (Nekrasov et al., 2019).

Botulinum neurotoxin (BoNT) was the target analyte of choice for Kim et al, who deployed a back-gated GFET to detect this toxic protein, responsible for causing fatal muscle paralysis (Kim et al., 2017). This device relies on antibody-antigen binding events to detect BoNT at a concentration of 1 μM. The linker *N*-hydroxysuccinimidyl pyrenebutanoate was used to immobilize monoclonal immunoglobulin G (IgG) to the graphene surface. Using Raman spectroscopy, this group showed that the linker molecule had caused both the G- (and 2D-) modes to redshift from 1590/cm (2649/cm) to 1585/cm (2646/cm), indicating *n*-doping of graphene. Subsequent immobilization of the antibody and BoNT showed no evidence of modes shifting and thus charge transfer to the graphene. Due to the difference in isoelectric points (pI) between the antibody and BoNT, with respect to the pH of the buffer solution, the molecules adsorbed on the surface of graphene formed charged layers which acted as additional top gates for this sensing mechanism. It was observed that the more negatively charged antibody layer would p- dope the graphene layer further, resulting in a larger I_{SD} at $V_G = 0$, whereas the positively charged BoNT layer caused a I_{SD} drop at $V_G = 0$ due to *n*-doping caused by the electrostatic gating effect. This GFET biosensor was able to show a normalized current change of 7% caused by the antibody-BoNT binding regime, an improvement from the 1% response demonstrated previously for AlGaN/GaN electrical sensors (Kim et al., 2017).

In an alternative approach, Liu's group immobilized single and double stranded DNA (ssDNA) and (dsDNA) using Au NPs, onto the graphene surface of their GFET, to facilitate the detection of bisphenol A (BPA), a chemical used widely for food packaging well known for its damage to the human and animal health (Liu et al., 2018b). This group exploited the fact that at high concentrations of BPA within a PBS solution, immobilized ssDNA and dsDNA bioreceptors were being removed from the graphene surface, due to the irreversible damage caused during the BPA-DNA binding events, Fig. 2 (C). When the probe ssDNA or dsDNA detached, the *n*-doping effect was reduced thus transducing binding and removal events as changes to the current in the channel. This group showed a LOD of 10 ng/mL, 5 times lower than the United State Federal Drug Administration's 50 ng/mL limit when dsDNA was immobilized on the GFET. As the graphene was not damaged during these sensing events, this group were able to re-immobilize ssDNA bioreceptors onto the GFET and repeat measurements demonstrating a reusable GFET biosensor, thus offering a significant cost reduction for their sensing strategy (Liu et al., 2018b).

An array of 36 liquid-gated GFET biosensors functionalized with ssDNA, was developed by Tu's group for the detection of mercury ions (Hg^{2+}), Fig. 2 (D). Mercury is a highly toxic material capable of impacting mammals' immune and nervous systems (Tu et al., 2018). Tu's group chose to deploy short DNA aptamers as bioreceptors in order to reduce the distance between the binding events within the electric double layer ensuring the ease of detection in the graphene sheet. In order to overcome variations caused by differences in graphene channels and low signal output observed for single GFET platforms, this group designed an array of GFETs which was designed to improve the acquired signal output and overcome inconsistencies. An electrostatic change caused during the binding events between the Hg^{2+} and the aptamers caused a rapid measurable response in the biosensor, of less than 1 s, with a LOD of 40 pM (the lowest reported from previous techniques), and a detection range of 0.1 to 100 nM. The selectivity of this biosensor array towards Hg^{2+} was investigated by monitoring the current response when other metal ions (Cu^{2+}, Pb^{2+}, Cr^{3+} and Cd^{2+}) were added to the liquid solution. The current through the device did not change significantly when the competing metal ions (at a concentration of 10 nM) were added and only changed when Hg^{2+} at a concentration of 100 pM (100 times lower) was added (Tu et al., 2018).

The high affinity of guanine-rich DNA towards Pb^{2+} was exploited by Chee et al, who used DNA bioreceptors attached to graphene by Au NPs to detect their presence using a GFET biosensor (Chee et al., 2017). Guanine-quadruplex (G-quadruplex) structures are formed when the negatively charged phosphate group of DNA causes it to encompass the positively charged Pb^{2+} ions. The initial left shift in the Dirac point caused by *n*-doping from the DNA immobilization was reduced when Pb^{2+} was added to the solution, forming G-quadruplex structures which increased the positive charge close to the channel subsequently p-doping the graphene and increasing the V_G of the Dirac point. Chee confirmed that Pb^{2+} had an insignificant impact on the Dirac point of graphene itself by comparing its position when guanine-rich DNA was and was not immobilized onto the graphene surface. These GFETs were able to detect the Pb^{2+} in deionized water (DIW) at a concentration of 20 nM, below the allowable concentration limit in drinking water of 50 nM as specified by the WHO (Chee et al., 2017).

3.3. Limitations to graphene field effect transistor sensors for detecting food adulterants and toxicants

Multiplexing GFET devices immobilized with different bioreceptors specific to distinct target analytes simultaneously will offer increased simplification for testing strategies. Hydrogels encapsulated with

different bioreceptors were patterned onto GFET channels by Bay's group as they showed the simultaneous monitoring of penicillinase- and acetylcholinesterase- functionalized hydrogels paving the way for future multiplexed GFET devices, Fig. 2 (E). These devices displayed additional benefits from using hydrogel environments as they prolonged the enzyme activity from a few days to one week and also showed a reduction in the nonspecific binding response when tested with BSA (Bay et al., 2019). In addition, quantifying the concentration of contaminants by measuring the shift in the Dirac point during electrical characterization is advantageous over other techniques (where only the presence or absence is determined), as it can be applied to scenarios where strict limits on the quantity of the adulterant is controlled and low levels are permitted.

High quality graphene exhibiting the most attractive properties such as mobility values reaching 250 000 cm^2/V s suitable for niche experiments and devices is surprisingly relatively straightforward and inexpensive to produce (Novoselov et al., 2012). However, difficulties in replicating such properties when producing graphene using other methods specifically when scaling up to large quantities is currently one of the bottle-necks for this material in becoming a truly disruptive technology for GFET biosensing applications (Forsyth et al., 2017). The CVD process is currently one of the best candidates offering cost-effective mass-production of 2D monolayer graphene suitable for GFET biosensing applications. Currently, this technique is limited by its high temperature/energy consumption and the additional processes required to transfer graphene from its metallic growth substrate onto users' desired supporting substrate, which has the effect of introducing additional contamination onto the graphene surface. Even with substantial developments in these areas, improvements with regards to the doping, layer number and grain sizes are also required to transition this technology out of research and into the industrial setting (Novoselov et al., 2012; Forsyth et al., 2017).

One other major consideration of GFET biosensors limiting their use in a practical environment is their stability with time. As graphene is so sensitive to its environment, understanding how handling, processing and storage techniques impact its electrical properties is essential to ensuring robust measurements of manufactured devices. It is well documented that graphene's exposure to the environment causes changes to its intrinsic properties (Yang et al., 2012). During a study led by Jia, a pristine back-gated GFET (~μm scale) was tested after being exposed to the ambient environment for one month (Jia et al., 2013). This group reported a shift in the Dirac point of their device illustrating the impact of the environment on graphene. Conversely, in a longer-term study, Chen investigated the electrical conductivity of a large area of CVD graphene (~mm scale) over the course of 500 days in an ambient laboratory environment. Chen's group observed excellent stability in their devices over this period of time, with interactions with the environment accounting for resistance oscillations of less than 10%. The surface morphology of the graphene also remained intact during this time period with no additional cracking or corrosion caused by exposure (Chen et al., 2018). Saltzgaber's group demonstrated that their GFET device, designed to detect the thrombin biomarker, was reusable and gave similar detection results after it was cleaned, left in an ambient environment for one week and then subsequently re-immobilized with fresh bioreceptors (Saltzgaber et al., 2013). This methodology could provide a solution for storing GFET devices although the stability of the immobilized bioreceptors then becomes of paramount importance. Clearly further work is required in order to develop the practical strategies for using GFET biosensors in industrial settings.

Improving the sensitivities past the limitations created by Debye screening is another hurdle for GFETs to overcome. Specifically, the development of immunoFETs, which rely on attaching antibodies onto the surface of graphene, has been restricted by Debye screening as their large physical size and higher ionic concentration levels, required to stabilize biologically active species, both acts to shift the binding event between antibody and antigen outside of the Debye length (Forsyth et al., 2017).

The incubation time for target analytes becomes more significant when considering the options of deploying GFET devices as real-time sensing platforms with either reversible or irreversible interactions. Applications that rely on monitoring the fluctuations of biomolecules in a continuous manner have been achieved by immobilizing bioreceptors that reversibly bind and discharge target analytes. The capturing and release events are transduced into modifications of the GFET current proportional to the concentration of biomolecule captured or released allowing longer-term detection regimes and reusable biosensors. Irreversible interactions whereby the strong binding between bioreceptors and target analyte prevents release are conventionally used for disposable or single-use sensing strategies where the simplification of use is of paramount importance (Donnelly et al., 2018). Therefore, a more thorough understanding of the incubation time and interactions between bioreceptors and target analyte is required for continuous monitoring situations where fluctuations in the analyte concentration may occur at a rate higher than the bioreceptor-target binding rates. When assay time is not a critical requirement for the sensing strategy, single-use irreversible platforms could be more appropriate.

4. Graphene-based electrochemical sensors

4.1. Electrochemical sensing mechanism

Electrochemical sensors have been widely used for monitoring food safety and quality. This type of sensor transforms the binding of specific chemical/biological molecules, which originate from food products, into a digital signal via electrochemical measurement. The characterization methods mainly include cyclic voltammetry (CV), differential pulse (DPV), square wave voltammetry (SWV), amperometry and electrochemical impedance spectroscopy (EIS) (Dincer et al., 2019). A typical voltammetry configuration consists of three electrodes, namely working, counter and reference. The desired linear, cyclic or pulse potential is sweeping between working and reference electrode, independent of the potential drop, whilst the current is measured between working and counter electrodes. Amperometry also employs three electrode configurations, but it gauges the redox current from the electroactive molecules at a constant (single-potential amperometry) or stepped potential (chronoamperometry), which is enough to oxidize or reduce the specific analyte. EIS sinusoidal potentials over a sweeping frequency are applied to measure the change of resistance and capacitance of the system, which is attributed by the binding of target molecules. This method is particularly useful for the characterization of resistive molecules on the electrode surface, as it does not require a large current flow between electrodes. The detailed waveforms and analysis methods have been summarized by Dincer's group (Dincer et al., 2019).

In a graphene electrochemical sensor, the surface of working electrode is normally coated by graphene nanomaterials and then functionalized by probe molecules, such as aptamer (Yin et al., 2017; Sun et al., 2017) as shown in Fig. 3 (A) and (B), antibody (Jijie et al., 2018), enzyme (Cao et al., 2013), which specifically bind to the target molecules. The electrochemical response mainly depends on heterogeneous electron transfer kinetics and electroactive area. Upon the binding with target molecules, the electroactive area or electron transport resistance of the sensor surface will decrease or increase depending on the charge condition and molecular resistance of the target molecules, resulting in the changes of redox currents and impedance. Using graphene-based nanomaterials as the sensor surface the electrons predominantly exchange at the crystal defects and edges of nanosheets (Li et al., 2015, 2016). Therefore, by employing graphene or rGO nanosheets as the electrode materials, a larger number of edges and defects can participate in the fast electron exchange, resulting in the improved sensitivities and LODs for detection.

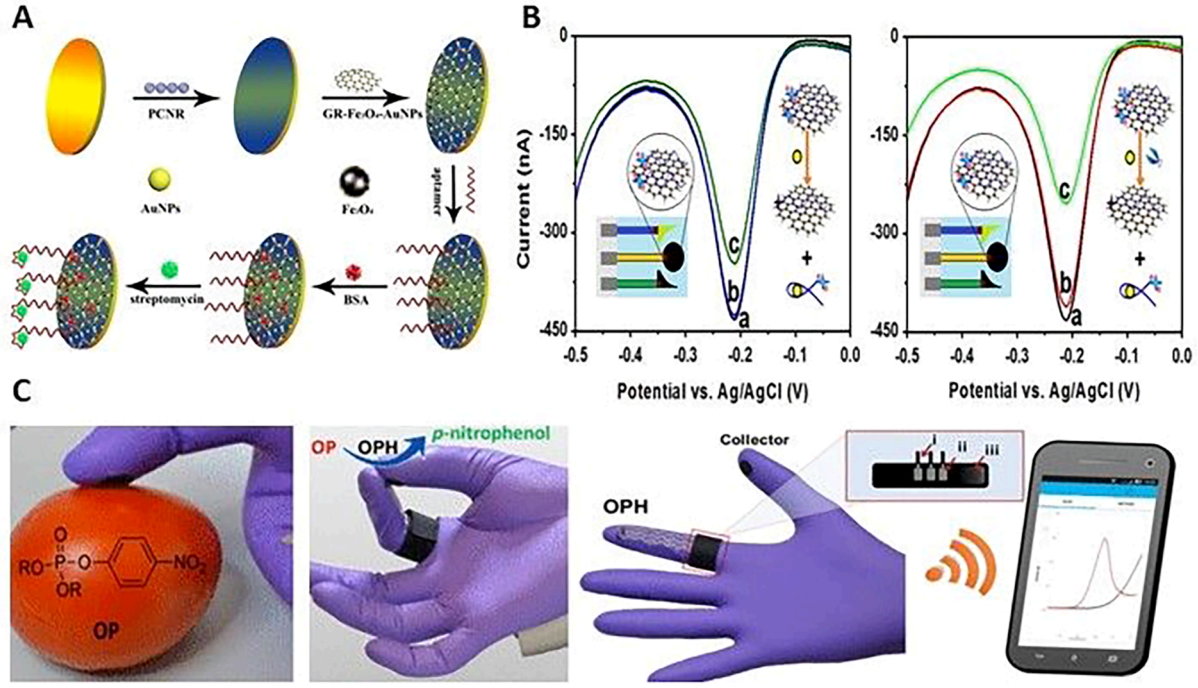

Fig. 3. Overview of electrochemical sensors for detection of chemical residues. (A) Schematic of electrochemical aptasensor for the detection of streptomycin. The Glassy carbon electrode (GCE) was functionalized using porous carbon nanorods (PCNR), graphene-Fe_3O_4-AuNPs nanocomposites, specific aptamer in order to recognise streptomycin. Reprinted with permission from Elsevier (Yin et al., 2017). (B) Left panel: DPV response (a) thionine–aptamer/graphene-modified screen printed carbon electrodes (SPCE), (b) electrode 'a'+zero ochratoxin A (OTA) and (c) electrode 'a'+10 ng/mL OTA in pH 7.4 (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) (HEPES) buffer; and right panel: DPV responses of (a) thionine–aptamer/graphene-modified SPCE, (b) electrode 'a'+DNase I and (c) electrode 'a'+10 ng/mL OTA + DNase I in pH 7.4 HEPES buffer. The decrease of peak current is lower in the presence of DNase I compared to the absence of DNase I for the same concentration of OTA. The results confirm the possibility of immobilizing thionine–aptamer on graphene oxide and DNase I could amplify the signal. Adapted with permission from Elsevier (Sun et al., 2017). (C) Flexible glove biosensors for the detection of chemical residues on surfaces. Showing the coupling protocol for sampling from tomato surface, and the on-glove sensing procedure by joining the index and thumb to complete the electrochemical cell. Connection potentiostat and glove sensor consists of; (i) wiring with potentiostat, (ii) aluminium-tape based pins for adjusting the ring with sensing connectors and (iii) velcro fabric. Adapted with permission from ACS publication. Note: Contact ACS for further use of this material (Mishra et al., 2017).

4.2. Applications in food safety

Pesticides are considered one of the most common contaminants in food products. They are intended to protect the crops from biological threats such as weeds, insects and fungi, however, remaining residues in high enough doses can become toxic to humans. Zhang et al developed a graphene electrochemical sensor for the sensitive and selective detection of imidacloprid residue (Zhang et al., 2017). In their work, p-vinylbenzoic acid was immobilized onto graphene via π-π bond and directly polymerized to form a molecular imprinted layer on the surface of working electrodes. This configuration presented a linear range of 0.5–15 μM with a LOD 0.10 μM for the detection of imidacloprid. Furthermore, Wang's group developed a screen-printed electrode, of which the surface was successively modified with graphene nanosheets, magnetic nanoparticle (Fe_3O_4) and acetylcholinesterase (AChE) for the detection of chlorpyrifos (Wang, 2016). With the presence of chlorpyrifos at different concentrations, the activity of AChE was inhibited differently. This sensing mechanism leads to a detection range from 0.05 ng/ml to 100 ng/ml with the LOD found to be 20 pg/ml. Although complicated nanostructures are believed capable to further enhance the electrochemical sensing performance (Li et al., 2020), the above method already provided competitive sensitivity compared to the gas chromatographic methods for the detection of chlorpyrifos in vegetable samples. Further to pesticides, mycotoxins and antibiotics are further examples of contamination commonly found in crop products. Geleta et al used MoS_2, polyaniline, Au NPs and aptamers for the functionalization of rGO modified electrodes and the detection of aflatoxin B_1 (Geleta et al., 2018). The rGO/MoS_2/PANI nanocomposites were first produced and deposited onto the electrode surface to enhance its electroactivity. Au NPs and aptamers were then introduced onto the electrode to further enhance the sensitivity and selectivity. This aptasensor exhibits a detection range of 0.01–1.0 fg/mL and a promising low LOD of 0.002 fg/mL. Yin et al developed an electrochemical aptasensor for the quantitation of streptomycin residues using a novel signal amplification strategy (Yin et al., 2017). In their design, the carbon nanorods were firstly deposited onto Au electrode as a base layer. Graphene nanosheets-Fe_3O_4-AuNPs complex was assembled onto the electrode surface as signal enhancer, followed by the functionalization of nucleic acid aptamer, Fig. 3 (B). The linear detection range and LOD for such sensors have been found to be 0.05–200 ng/mL and 28 pg/mL. These two studies show that multiple signal enhancers play a significant role in increasing the sensitivity of electrochemical sensors. However, it is noticeable that the multi-stepped functionalization using complex nanomaterials normally leads to reduced reproducibility and stability. A trade-off has to be made between the higher detection sensitivity and the lower device complexity. Other food contaminations, including nitrates (Ali et al., 2016), metal ions (Priya et al., 2018) and *E. coli* (Wang et al., 2013b), have also been successfully detected using graphene-based electrochemical sensors proving its broad application in the field. Antimicrobial peptides (sAMP) are engineered for the detection of live or dead bacterial pathogens such as *E. coli, P. aeruginosa, S. aureus* and *S. epidermidis*. Electrodes modified with sAMP show promising detection sensitivity using CV (Liu et al., 2016).

In addition to the food contaminations, artificial additives are of increasing concern in food products. Synthetic aromatic azo dyes, such as Sunset yellow (SY) and tartrazine (TT), have been some of the most commonly used additives in the food industry. Excessive use can be harmful causing allergies, migraines, diarrhea and even cancer (Rowe &

Rowe, 1994). Gan's group demonstrated an electrochemical sensor to simultaneously detect SY and TT using graphene-wrapped phosphotungstic acid hybrid active composite (Gan et al., 2012). Gan demonstrated high electron transfer mediation on GCE and presented the LODs of 0.5 ng/mL and 30 ng/mL for the detection of SY and TT respectively, which is compatible with their HPLC results obtained in the same work. Preservatives, such as caffeic acid, caffeine, ascorbic acid, sulphite and nitrite form another category of artificial additives, designed to prevent food spoilage. Jiang et al. developed a graphene-AuNP-Hemoglobin (Hb) composites functionalized electrochemical sensor for the determination of nitrite (NO_2^-) (Jiang et al., 2014). The sensing mechanism is the same as when NO_2^- binds to Hb in vivo, which shows a LOD of 0.01 μM developing the detection of NO_2^- in pickled radish samples.

4.3. Barriers to electrochemical sensors in point-of-need detection

Electrochemical sensors are one of the most promising techniques for the detection of chemical and biological molecules to ensure food safety. Compared to the well-established methods in laboratories, such as liquid chromatography and MS, the point-of-need electrochemical sensors could potentially provide accurate enough results within minutes at a relatively low cost. However, there are barriers to the practical use of point-of-need mainly attributed to the low reproducibility of measurement and the complexity of sample preparation.

The low reproducibility of electrochemical measurement is caused by many factors, including the lack of a unified standard for producing graphene-based electrodes. Sensors prepared by different manufacturers use their own methods or materials with a wide spectrum of responses during experimental measurement, even when the sensors are exposed to the same target molecules. This causes complexities in baseline calibration and data cross-validation. In addition, the electrochemical sensors require a liquid sample or liquids extracted from solid foods. The processes of extracting, purifying and enriching the target molecules from food products are challenging to be performed at point-of-need sites without the laboratory setting. Furthermore, the target concentration in analyte samples will not only depend on the aforementioned extraction methods, but user operation and environmental factors (for example, performing electrochemical measurement near other electrical equipment will pick up significant noise), leading to invalid results. A standard operating procedure (SOP) will need to be developed for sample preparations and a step-by-step characterization and calibration process would be issued with each sensor for data harmonization.

5. Strategies for integrating graphene-based sensors into portable devices

Portable detection systems require good performance metrics, such as sensitivity, specificity, ease of use, cost, power consumption, footprint, scalability, and ruggedness. The three primary measurement mechanisms reported, optical, electrical and electrochemical have their own merits and drawbacks for field usable systems and therefore require careful evaluation as to their suitability. This section highlights the importance of three techniques and their strategies for integrating into portable devices. Table 3 summarizes the advantages and disadvantages of graphene-based optical, electrical and electrochemical sensor techniques.

Table 3
Summary of graphene-based optical, electrical and electrochemical techniques.

Category	Technique	Advantages	Disadvantages
Optical	Fluorescence	Natural fluorescence in vitamin and amino acids can be detected at a very low concentration achieved by conventional light sources	Interference from intrinsic fluorophores among food products (ex. edible oils, dairy products, fish) Some products require complicated sample preparation process like precipitation and extraction
	SPR	Real-time analysis and rapid testing is possible Requires very small quantity of sample	Design of sensor is a meticulous process and expensive Limitations during mass transport. Influence of non-specific binding to surfaces
	SERS	No need for sample pre-processing and works at wide range of temperature values. High spatial resolution	Interference from intrinsic fluorescence in several food products Target needs to be deposited on SERS substrate
Electrical	Back-gated GFET	Dry measurements simplify fabrication process and device integration Vapor detection possible Suitable when detecting targets in solutions with varying compositions	Thick oxide layer requires high back-gate voltage to see ambipolar behaviour (±20 V)
	Liquid-gated GFET	Thin electrical double layer reduces top-gate voltage required to see ambipolar behaviour (±0.1 V) Microfluidic structures suitable for storing complex buffer solutions required for stabilising biological species	Shorter bioreceptors required to overcome Debye length caused by electrical double layer Instability from using ionic buffers to form electrical double layer
Electrochemical	EIS	No requirement for current passing, suitable for insulating layer measurement Enable measurement at specific frequency	Complicated curve fitting analysis
	CV	Fast setup and easy operation	Less sensitivity when electrode covered by insulting layers
	DPV, SWV	Very sensitive due to the removal of charging current	

5.1. Optical techniques for portable devices

Optical methods exploit some unique properties of graphene and its derivatives. The most peculiar property is high (up to 100%) (He et al., 2010) quenching efficiency via FRET, conjugating fluorescence based biosensing molecules (Deng et al., 2014) with graphene acting as both fluorophore donor and acceptor, which enhances its utility (Morales-Narváez & Merkoçi, 2012). Optical absorption-based measurements using graphene are not as well reported due to its low optical absorption (2.3% per layer) (Li et al., 2019a). However, plasmonic hybrids have been reported with good performance (Deng et al., 2014). These include SPR, SERS, polarization absorption and colorimetry. Optical methods demonstrate high tolerance to environmental vibrations and electrical noise characteristics that are essential for the development of portable devices. Fluorescence based miniaturized measurement systems have been reported. These include systems that use mobile phones for read out - such as graphene quantum dots (GQDs) based fluorescence nanoprobes for analysis of nitrophenols (El-Shaheny et al., 2020); ethylenediamine functionalized graphene oxide (EDA-GO) for Cd^{2+} ion detection (Wang et al., 2020a); Zn detection using mRNA on GO (Giust

et al., 2018) and GQDs for pM level antibiotic detection in food samples (Ye et al., 2020).

There are reports of portable Raman spectrometers being used, such as for detecting drug residues using graphene oxide coated Ag nanoparticles (Maofeng Zhang et al., 2019); Rhodamine B in chilli powder using CuSe-rGO (Moreno et al., 2019); pesticide residues in banana peel using TiO_2–Ag–GO substrate (Maofeng Zhang et al., 2018); freshness of fruits via Au and Ag NP conjugated with graphene (Gopal et al., 2016). Some other methods include electrically induced chemiluminescence for *E Coli* detection using GQDs (Li et al., 2019b) and antibody coated graphene for *E. Coli* detection using a lateral flow strip (Morales-Narváez et al., 2015).

Optical methods seem to be best suited to portable devices due to their higher ruggedness and non-contact nature. However, further progress is needed towards construction of low-cost fluorescence detection systems to enable true field usable devices. In this context, the ever-falling cost of optoelectronics and availability of a wider range of programmable systems are quite promising. Further, emerging technologies such as 3D printing can be of great use for researchers since they can allow the rapid prototyping and field testing of low-cost sensors (Rocha et al., 2020).

5.2. Electrical techniques for portable devices

The electrical method utilizes graphene and its derivatives in a FET or a chemi-resistor format benefiting from the highly developed semiconductor manufacturing processes with the potential to be low-cost and scalable. FET based systems with mobile phones or similarly sized units have been reported for cytokine biomarkers in saliva via aptamers (Hao et al., 2019) and Pb^{2+} detection as low as 1 ppb (Maity et al., 2017). GFET biosensors offer several advantages over other detection regimes which are particularly suitable for portable devices, specifically, GFETs' mechanical flexibility, small size and compatibility with current semiconductor fabrication techniques all promise great things for the future of portable biosensing platforms (Donnelly et al., 2018). The mechanical strength of graphene has been exploited by Petrone's group into producing flexible GFETs that are paving the way for future wearable technologies (Petrone et al., 2015). Flexible GFETs with graphene encapsulated in hexagonal boron nitride, were developed by this group to test how the mechanical strain impacted the device characteristics. They showed that their GFETs on the highly flexible polyethylene naphthalate substrate could withstand a strain of 1%, with only a 13% degradation in the field effect mobility between the unstrained and 1% strained states (Petrone et al., 2015). In a similar detection strategy that Mannoor et al. demonstrated for wirelessly monitoring bacterial growth around hospitals using wireless graphene-based biosensors (Mannoor et al., 2012), small, low-cost, flexible GFET tags, could be deployed to conform to food/water processing equipment that are distributed across an industrial setting. Tags could then be interrogated with a low-powered, portable, hand-held device which interfaces directly to them, relieving the need for the tags to have their own supporting electronics and power supply.

However, three major challenges exist to this detection strategy which currently limits its use in everyday ultrasensitive sensors. Firstly, the lack of overall ruggedness – FET based devices are more sensitive to environmental disturbances. Secondly, in order to reach the highest of sensitives that GFETs currently promise in the future the 1/f noise, endemic to electronic devices and which dominates the noise contribution of GFETs at biologically relevant frequencies, requires further investigation. Careful circuit design and operation is one technique to reduce the influence of this particular noise on this detection strategy (Zhang et al., 2020). Finally, the cost of acquiring good quality monolayer graphene driving up fabrication costs. Advancements in CVD technology have provided large areas and thus cost-effective products with mobilities in the region of 1000–10,000 cm^2/V s (Fu et al., 2017).

5.3. Electrochemical techniques for portable devices

Screen printing techniques, which use graphene inks to define sensor geometries, have facilitated large-scale, low-cost and disposable sensing strategies (Taleat et al., 2014). Screen-printing deposits graphene inks onto a solid substrate through a pre-patterned screen, defining the geometry of the sensor component. However, the quality, such as the adhesion of graphene ink layer and the stability of dielectric layer in organic solvent, need to be closely monitored to ensure the sensors provide good reproducibility throughout the analysis (Cinti & Arduini, 2017). Furthermore, other food adulterants have not yet been investigated or cannot be detected at low concentrations due to the inadequate sensitivities caused as a result of a high density of grain defects and oxygen-containing residues on graphene nanosheets (Tian et al., 2017). Therefore, proper signal amplification, which can be adopted to the point-of-need applications, has been considered an essential strategy to achieve higher sensitivity. Signal enhancement achieved by integrating extra procedures requires corresponding equipment, agents, expertise and some processing time, which will increase the sample-to-result times for accelerating intervention. In addition, another challenge is to develop a low-power, miniaturized potentiostat (Bobrinetskiy & Knezevic, 2018) for performing the point-of-need measurements. There are reports of systems using the miniature potentiostats, but are hampered by large power consumption and are application specific lacking versatility. An emerging trend to address this issue is the smartphone-assisted diagnostics (Quesada-González & Merkoçi, 2017). Smartphones are ubiquitous across all the countries with cameras, powerful microprocessors and short/long range wireless communications capabilities. For example, inexpensive plug-and-play smartphone-based electrochemical analyzers have been implemented for portable sensors as shown in Fig. 3 (C) (Mishra et al., 2017). These can be directly powered by the smartphone's battery or the energy harvested from the smartphone (Sun et al., 2016). Continuous improvements in the device miniaturization, interface optimization and data analysis algorithms will encourage the development of smartphone-assisted graphene food sensors.

Credit card sized electronic systems with integrated potentiostats have been reported for a variety of contaminants. These usually use SPE containing functionalized graphene or its derivatives. These include NP based sensors for detecting nitrites in water (down to 0.1 μM via Au NP-rGO) (Xu et al., 2020); Sn and Pb in water (as low as 10 ng/mL using BiNP-GR) (Pungjunun et al., 2020). Aptamer based sensing has been reported for arsenite detection (Zhou & Tang, 2018). Others such as pyrrole-based sensing for cortisol (Torrente-Rodríguez et al., 2020) and even chicken breast meat freshness using graphene enhanced electrodes (Fu et al., 2019) have been reported.

The choice of measurement methods is key to portable devices. While electrochemical methods have been reported the most in scientific literature, the difficulty in making low power and versatile potentiostats limit their utility in portable systems.

6. Conclusion and future scope

Detecting adulterants and toxicants in food products requires robust sensors with high reproducibility. These sensors should be reliable and produced at a large-scale to manage mass screening of ever-increasing sample numbers. This review highlighted the importance of graphene-based sensors for detection of contaminants and adulterants in food products. The advantages and limitations of graphene-based sensors for target detection using optical, electrical and electrochemical techniques are illustrated with the specific challenges relating to each method discussed. Integrating graphene sensors into portable devices is an essential task to realize these sensing strategies as disruptive technologies for practical settings, bridging the gap between research laboratories and industry. The sensors must be robust and be able to withstand interference from various environmental parameters to fit into field-

usable devices. Further developments in device miniaturization, real-time data analysis and smartphone-assisted sensing technologies are some of the routes that will hasten the uptake in use of these sensing strategies. Considering all that is discussed herein, it is envisaged that graphene-based sensors have numerous exciting avenues for maturing into practical devices for the detection of adulterants and toxicants in food products in the near future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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