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Recent Developments in Carbon Sensors for At-Source Electroanalysis

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Our understanding of the world around us has been greatly enhanced by our ability to detect and quantify analytes in the environment and in biology. It is highly beneficial to perform analysis at the site of interest, as many situations do not afford the luxury of time required for samples to be collected and sent for analysis. Some processes necessitate immediate detection to facilitate rapid action. As an example, harmful environmental phenomena can result from dynamic events, such as the recent spate of tropical cyclones in the Caribbean and Southeastern region of the United States. These storms have mobilized nutrients, facilitating large-scale algal blooms that are damaging to marine ecosystems and human health. The rapid delivery of analytical information during such events is the key to quickly mitigating detrimental effects. Another example is analytically monitoring the quality of drinking water in the context of avoiding residential crises such as in Flint, Michigan, where residents were exposed to high levels of Pb. Other examples include monitoring airborne workplace hazards with smart wearable devices and point-of-care (POC) diagnostics for monitoring health. An excellent, low-cost, and portable approach to measurements at the location of interest is electroanalysis. Specifically, carbon-based electrochemical sensors offer a versatile, chemically functional, and (bio)-compatible platform for detecting a variety of analytes. Carbon is utilized in many forms including graphene, composites, and fibers. With carbon-based sensors, scientists are creating novel electroanalytical devices that are greatly improving the speed and quality of at-source detection.

Every year researchers develop innovative carbon-based technologies for analytical sensors. Many of these sensors fail to make successful real-world measurements, because it is highly challenging to take analysis outside the lab. Measurements in real samples require high sensitivity, stability, and reproducibility. In addition, the out-of-lab environment is harsh, noisy, has variable temperature and pressure, and limited opportunity for sample preparation. Nonetheless, cutting-edge sensing advancements have tackled these challenges and are enabling at-source detection of an array of important analytes. In the proceeding article, we start by outlining the challenges of analysis at the site of interest. Subsequently the suitability and characterization of carbon for on-location electroanalysis is discussed. Then, we review novel carbon materials and/or devices for measurements of analytes for various applications, limited to environmental and process/manufacturing, biological measurements, POC diagnosis, and wearable sensors.

Throughout this review, we highlight the important role that carbon is playing in revolutionizing the speed, quality, and manner in which analytical information is delivered at the site of interest.

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CHALLENGES FOR AT-SOURCE MEASUREMENTS

Modern analysis methods are clearly very effective; however, these strategies are not always rapid, efficient, or implementable outside of a lab. Spectroscopic analysis often requires costly, bulky instrumentation with high energy needs. For ambient chemical analysis in the environment, this type of analysis is prohibitive in situations that have limited access. addition, spectroscopic analysis, for the most part, requires sample collection and preparation, which is time-consuming, impractical, and fundamentally alters the speciation information that is critical for assessing pollution or contamination risk. Many health-care practitioners, hospitals, and industries do not have adequate analytical laboratories and must outsource analysis. For the facilities that have on-site analytical laboratories, information is often not delivered quickly, with hours or days required. Additionally, skilled laboratory personnel are required for sample collection, preparation, and data runs.

Consequently, chemical detection at the site of interest is greatly desirable, and, while the benefits of on-site data collection are evident, detecting analytes outside of a laboratory setting provides a host of complications. Factors such as portability of instruments, energy, accessing samples, noise, technical skill, pressure, temperature, humidity, convection, ionic strength, pH, and sample contamination are but a few issues to address. Electrochemical analysis has made important strides in recent years to tackle these issues and provide easy-to-use measurement devices. This is because the fundamental analysis occurs at a substrate (electrode) that c be fashioned into an immersible form, directly probing the sample of interest or integrated into a compact portable analytical device. Carbon is a particularly popular substrate material for this kind of analysis for a variety of reasons, which are outlined in the following section. For the majority of cited works, we focus on carbon as the direct detection surface; however, we do add examples, where no other alternative exists, of enzymatically or otherwise modified carbon electrodes.

CARBON AS A VERSATILE AND SUSTAINABLE ELECTRODE MATERIAL FOR AT-SOURCE MEASUREMENTS

Carbon is an excellent electrode material because of its relative inertness, workability, economical cost, wide potential window, excellent electrochemical properties, and rich surface chemistry. Carbon's abundance versus other popular electrode materials like platinum and gold make carbon arguably the most popular electrochemical substrate.

Carbon's availability has largely driven the conceptualization of at-source, disposable, or single-use sensors, which has revolutionized in situ analysis and POC diagnostics.[1−7] However, with the recognition that even carbon is a finite material, there has been a push to develop "green science" strategies of transforming waste materials into useable carbon electrochemical substrates. This section first highlights recent fundamental studies that have characterized the effects of molecular defects and contaminants on carbon reactivity and outlines recent developments in ultrapure carbon surface analysis. Next, recent developments in electrode fashioning modification are discussed. Finally, "green" methods of deriving carbon electrodes are presented.

Characterization of the Carbon Surface. Understanding the fundamental chemistry and reactivity of the carbon surface is essential to developing better sensors. This is especially important when attempting to make measurements at-source, out of the controlled lab setting. Carbon exhibits favorable electrochemical characteristics that are dependent on microstructure and overall morphology, unlike most metal substrates, which exist as a single underlying entity. Carbon surfaces are robust and relatively inert facilitating an ideal platform for heterogeneous electron transfer.

Despite carbon's relative inertness, this material is still susceptible to surface contamination that can substantially affect electron transfer processes. One strategy to studying the effects of contamination is to examine the ultraclean carbon surface. Scanning electrochemical microscopy (SECM) is a popular technique used by electrochemists to analyze electrode surfaces.[8,9] To characterize carbon surfaces a standard redox system, $Ru(NH_3)_6^{2+/3+}$, is often analyzed to determine the transfer rate constant k°.[10,11] Figure 1A is a schematic of the layer deposition and thickness of electron beam deposited carbon on Au/TiC surfaces originally reported by Amemiya, McCreery, and colleagues. The voltammetric setup is displayed in Figure 1B. The carbon films are protected by a thin layer of KCl to prevent any surface contamination prior to electroanalysis thus ensuring ultraclean electrochemical surfaces (Figure 1C shows atomic force microscopy (AFM) images of the surface before and after KCl layers; the AFM surface scan profiles of the two surfaces are in Figure 1D). This method generates an ultraflat (<1 nm roughness), pristine carbon surface.[12,13] These carbon films have been used to determine very fast k° values compared to Au, Pt, carbon nanotubes (CNTs), and highly oriented pyrolytic graphite (HOPG) as well as show evidence of self-inhibitory electron transfer caused by adsorbed redox species electrostatically blocking activity.[12,13]

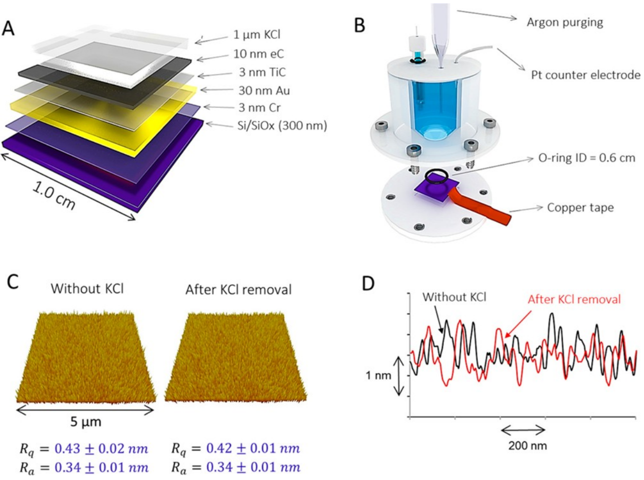

Figure 1. (A) Schematic representation of the layer deposition and thickness on 1.0 cm² substrate. (B) Schematic of electrochemical cell for voltammetry experiments. (C) AFM images of surface with KCl protection layer and after removal of KCl. R_a and R_q are average and root-mean-square roughness, respectively. (D) AFM surface scan profiles of the two surfaces in (C). Reproduced from Morteza Najarian, A.; Chen, R.; Balla, R. J.; Amemiya, S.; McCreery, R. L. Analytical Chemistry 2017, 89, 13532−13540. Copyright © 2017 American Chemical Society.

The major contaminants of carbon surfaces are adsorbed hydrocarbons, although trace organic impurities from ultrapu water can also decrease electrochemical activity.[14−18] When designing a carbon sensor destined for real-world analysis, the potential for unintentionally compromising surface activity must be considered. Knowing that a pristine carbon surface is nearly unachievable in a real-world setting, because ambien affects electroactivity, highly effective polishing strategies have been explored. High-vacuum annealing and ultraviolet-O$_3$ treatment have been explored as methods to remedy ambie air-effected exfoliated HOPG, but adsorbed contaminants w only partially removed.[14,15] Exposing the graphene surface to hydrogen plasma for a short duration (1 s) drastically improved the kinetics (~12 fold) of the Ru(NH$_3$)$_6^{2+/3+}$ redox couple, credited to H· reacting with and removing adsorbed hydrocarbons, thus revealing a pristine graphene surface.[18] However, longer hydrogen plasma exposure resulted in increased sp^3 defects, which decreased k° but preserved electron mobility showing promise for future use in graphene field effect transistors.[18] While highly effective, these methods likely cannot be extended to real-world sensors. At-source sensors should be designed knowing that surface contamination is unavoidable and must either be sensitive enough to perform in the presence of surface contamination or be cleaned with appropriate, available polishing techniques.

A strategy to improve sensitivity or selectivity in the absence of ultrafine polishing is to modify the carbon surface, which we discuss below.

Creating and Modifying the Carbon Surface. The ease with which carbon can be chemically and physically modified is another key advantage of this material. The following section highlights recent reports that provide information on the carbon surface and details modifications of carbon for analysis.

There are some recent reports of improving carbon fabrication processes. Traditionally, chemical vapor deposition (CVD) on Cu foil with a support polymer, commonly poly(methyl methacrylate) (PMMA), has been the primary method for creating graphene sheets.[19−21] Chen et al. recently developed CVD-based fabrication of graphene substituting polystyrene for PMMA as the polymer support.[22] This modification yielded a 2−3 times rate increase for ferrocenemethanol redox coupling analyzed by SECM nanogap voltammetry compared to PMMA-transferred graphene. In other work, Akinoglu et al. published a 2018 report detailing plasma-enhanced CVD of CNTs on glassy carbon electrodes (GCEs). These textured electrodes have an interesting characteristic such that, as scan rate is increased, the peak-to-peak separation trends toward ideal thin-layer diffusion.[23]

Carbon composites are interesting materials in that they adhere the characteristics of other materials to carbon. The Henry lab has developed new carbon composite electrodes coined “thermoplastic electrodes” or TPEs.[24] These electrodes are low-cost and consist of a thermoplastic binder that results in a malleable conductive material when heat pressed that can be embossed, molded, templated, or cut via CO$_2$ laser for precise fabrication. Not only is this material easy to fashion, TPEs exhibit an improved ferricyanide peak current and peak separation compared to Pt, glassy carbon, and screen-printed electrodes (SPE). Scanning electron microscopy (SEM) images following plasma polishing, shown in Figure 2, reveal areas of graphene-like exfoliated graphite, which supported TPEs electrochemical performance under optimized conditions rivaling that of graphene's.[24]

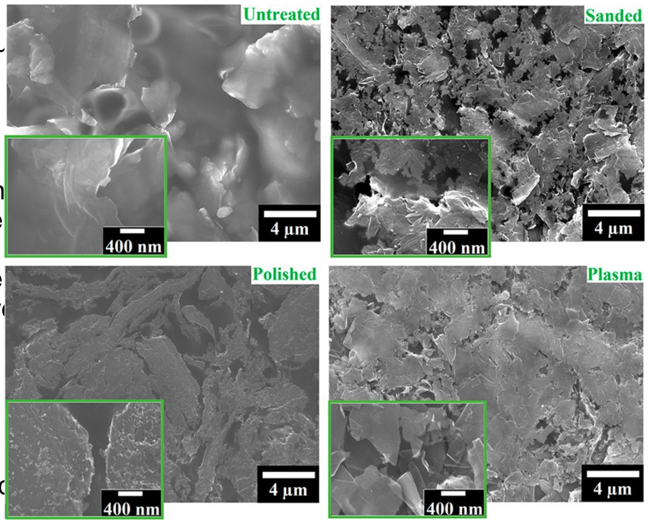

Figure 2. SEM images at 5000× of a 1:2, 11 um TPE. (top-right) Untreated surface; (top-left) after being sanded with 600 grit paper; (bottom-left) after being polished with 0.05 um alumina microfiber pad; (bottom-right) after plasma treatment of 35 W for 3 min. Reproduced from Klunder, K. J.; Nilsson, Z.; Sambur, J. B.; Henry, C. S. Journal of the American Chemical Society 2017, 139, 12623−12631. Copyright © 2017 American Chemical Society.

Carbon is traditionally thought of as a hydrophobic material. However, recently there has been evidence supporting the hydrophilicity of graphene's surface when analyzed at the atomic level.[16,25,26] Freshly exfoliated HOPG was stored at low temperature to investigate hydrocarbon adsorption, where it was determined that a nanometer thick layer of water−ice was present that preserved electrochemical integrity by inhibiting hydrocarbon adsorption.[16] This result was further strengthened when Akaishi et al. used molecular dynamic simulations to explore how a graphene surface with no adsorbed hydrocarbons would interact with water molecules.[25] They showed that a bilayer of water molecules was formed exclusively via hydrogen bonding on the surface. This, now hydrophobic surface, has little effect on graphene electroactivity[18] and is one mechanism by which contaminating hydrocarbons adsorb. This finding has the potential to broaden the applicability of graphene with a surface tailored to be either hydrophilic or hydrophobic.[26−32]

Diamond is a unique carbon allotrope that can act as a semi- or fully conducting material depending on the type and amount of dopant present.[33] A relatively new and exciting field has been the application of diamond films to electrochemical analysis.[34] Diamond has a wide potential window, and both cathodic and anodic scanning have been explored for analysis.[35−38]

Functional groups on diamond surfaces represent sites that can be chemically targeted to modify the electrode. Changing the termination groups, H- or O-terminated, on the diamond surface can greatly improve electroanalytical performance.[35,39−41] In 2015, scanning electrochemical cell microscopy was used to both functionalize boron-doped diamond (BDD) film and evaluate the effects of surface termination alterations on electron transfer.[42] Diamond can also be fashioned into a composite material.[43,44] For example, the Henry lab recently reported a BDD paste electrode with lower background currents and improved electrochemical characteristics compared to traditional carbon paste electrodes (CPEs) and demonstrated applicability for the detection of bioamines and heavy metals via a micropaper-based device.[45] Ongoing challenges include inconsistent k° values associated with heterogeneous dispersion of B atoms in BDD films, a feature that creates regions of high and low electrode activity.[46−49]

Covalent modifications, while not common, have been made to carbon fiber microelectrodes (CFMs),[50] CPEs,[51] GCEs,[52,53] CNTs,[54,55] and SPEs[56,57] for increased sensitivity and selectivity for heavy metal detection.

Sustainable Carbon. Sustainable or green chemistry focuses on limiting the use of harsh reagents in chemical synthesis, utilizing environmentally friendly reagents, and the efficient use of finite materials. An interesting example of sustainability is a recent drive to convert biowaste into activated carbon. However, functionalizing biomass is not trivial and requires the activated carbon to have optimized morphology and structure.[58]

The Zhou lab have been exploring several different biomass starting materials for creating carbon sensors. Pomelo peels,[59] kelp,[60] cherry husks,[61] and apples[62] have been converted into carbon nanoballs, mesoporous carbon, carbon nanoplates, and carbon nanorods, respectively. When deposited onto GCEs, each respective material displayed improved electrocatalytic activity, higher sensitivity, and a wider linear range than unmodified GCEs or CNTs-GCEs for hydrogen peroxide detection. Peanut shells and dandelions have also been used to create activated carbon materials for glassy carbon composite electrodes with increased electrocatalytic traits.[63,64] Kampioti et al. recently reported the fabrication of nanographitic rubber composite electrodes formed from natural rubber and nanographitic carbon sourced from food waste.[65] The composite electrode showed higher conductivity at much lower carbon loading (~10%) than previously reported composite sensors.[65] While these represent just a few examples of biomass materials used for electrochemical sensors, it is easy to envision the endless possibilities of potential biomass starting materials, given they are carbon-based. As more biomaterials are screened, starting materials will emerge that exhibit unique capabilities due to their specific chemical structures. One example is an S-doped reduced graphene oxide (rGO) sensor that capitalizes on lenthionine (organosulfur compound present in shiitake mushrooms) to provide highly sensitive detection of an oxidative stress biomarker 8-hydroxy-2′-deoxyguanosine.[66]

MONITORING AMBIENT CHEMICALS

There are countless scenarios during which it is useful to have on-location chemical sensing of the ambient environment. For example, extrinsic, detrimental chemicals can be released into the environment via aging infrastructure, industrial effluent, storms, and agricultural runoff.[67−69] Naturally present hazardous chemicals can also be unintentionally mobilized into natural waters.[70] In these scenarios, it is critical to obtain chemical information rapidly, at the site of interest to most effectively apply mitigation strategies. Certain industrial workplace environments contain intrinsic hazards, having the capacity to monitor chemical thresholds is a critical safety measure.

Monitoring on-site necessitates a specific set of criteria. The ideal sensor should be selective for the analyte of interest and display a fast response. A portable sensor should be small enough for easy transport, cost efficient, and have an internal power source for remote location sensing. Specifically, wearable sensors ideally ought to be self-powered, but they should also be flexible and durable for practical use and wearability. Finally, analysis methods should be capable of measuring at or below situation-relevant detection limits. For instance, sensors for industrial workers that detect harmful chemicals should have limits of detection (LOD) below the exposure limits set by the occupational safety and health administration (OSHA).

Within this section, we will focus on sensors for on-location measurements in air, soil, water, and food and drink. Because on-site sensors are still rather limited, we also highlight the development of sensors that have promise for incorporation into portable sensing devices. Within these categories, a variety of analytes present significant importance for monitoring pollution, climate change, contamination, and industrial processes. This section will focus on metals, pesticides, nitrate, pharmaceuticals, ammonia, volatile organic compounds (VOCs), and several other chemicals of interest to ambient monitoring.

Air. Monitoring air quality is unquestionably critical. Air quality reports inform people with respiratory issues if it is safe to go outside, and canary sensors in industry inform workers if there are acute hazards. Electrochemical measurements in gaseous media are more challenging than in solution, primarily due to uncontrolled parameters such as humidity and temperature.

Nitrogen dioxide (NO_2) is harmful to human and environmental health. As such, there have been recent efforts to develop a sensor to monitor release of NO_2, especially in the context of human exposure in industrial settings. Carbon is not a new substrate for NO_2 sensing; however, recent developments are enabling sensitive and inventive detection platforms. Kumar et al. demonstrated, for the first time, transfer of graphene directly onto paper without any intermediate layers by CVD. The use of glossy paper, rather than typical printing paper, results in a smooth and consistent layer of graphene. The paper sensor is then connected using conductive silver paint to a light-emitting diode (LED), which is illuminated when the sensing current resulting from NO_2 presence is detected. Overall, the sensor is both flexible and has a very low detection limit of 300 ppt (parts per trillion). Furthermore, the recovery time of the graphene paper is improved to just 30 s by exposure to deep UV light between NO_2 measurements.[71]

For workplace applications, wearable sensors are practical and useful. Power sources are a limitation for wearable/portable devices. One research group has focused on combining stretchable, patterned graphene and a micro-supercapacitor to develop a body-attachable sensor. The number of graphene lines included in the pattern determined the electrical resistance and are therefore optimized for good sensitivity to NO_2. Once optimized, the graphene sensor was integrated onto a specially designed Ecoflex substrate along with 12 parallel-connected micro-supercapacitor arrays. The authors continue to work to improve the temperature range in which the sensor is capable of detecting NO_2 as well as the lifetime of the device.[72] Lee et al. have taken wearable sensors one step further and incorporated rGO-based yarn directly onto fabric, as seen in Figure 3. Graphene oxide (GO) is incorporated into the yarn using an electrostatic self-assembly wrapping method mediated by bovine serum albumin and a low-temperature reduction. Figure 3a is a schematic of the rGO yarn sensor, showing interactions with O, N, C, and H. The yarn is selective for NO_2 to a limit of 1.25 ppm and

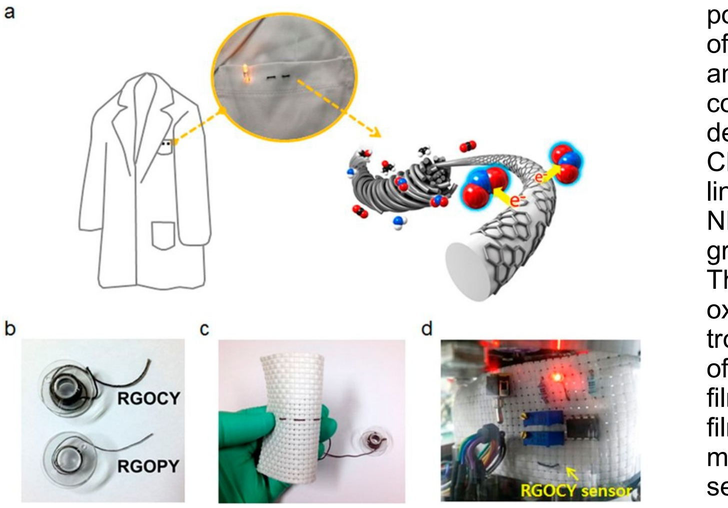

Figure 3. (a) Schematic illustration of rGO yarn gas sensor prepared from microfiber bundles wrapped with rGO. The interactions with oxygen, nitrogen, carbon, and hydrogen atoms are shown. (b) Photograph of rGO cotton yarn and rGO polyester yarn wound on a plastic bobbin. (c) rGO cotton yarn woven into fabric. (d) Configuration of the wearable gas sensor and LED system. Reprinted by permission from Macmillan Publishers Ltd: *Scientific Reports*. Yun, Y.; Hong, W. G.; Choi, N.-J.; Hoon Kim, B.; Jun, Y.; Lee, H.-K. *Scientific Reports* 2015, 5, 10904. This work is licensed under a Creative Commons Attribution 4.0 International License, copyright 2015. http://creativecommons.org/licenses/by/4.0/.

demonstrates flexibility and stability even after several detergent wash cycles. Figure 3b shows photographs of rGO cotton yarn and rGO polyester yarn wound on a plastic bobbin. In Figure 3c, the rGO cotton yarn woven into fabric, to be sewn into the pocket of a lab coat, which houses the electrical components. When the yarn is exposed to 5.0 ppm of NO_2, the OSHA exposure limit, it triggers an LED light, shown in Figure 3d, to alert the wearer of the hazard. While efforts to improve both the response and recovery time are ongoing, a yarn-based wearable is very promising for use in an industrial setting.[73]

VOCs are also dangerous to the environment and human health. They are often used and produced by industrial processes and are required to be monitored in the workplace by OSHA standards. Carbon composites have recently been used for the detection of VOCs. Specifically, a composite sensor was developed combining the selectivity of calixarene and the conductivity of CNTs by a noncovalent functionalization of single-walled CNTs (SWCNTs) with calixarene. The resulting sensor array is capable of measuring toluene, ethylbenzene, and xylenes at detection limits between 4 and 7.5 ppm, well below the OSHA exposure limits.[74] Alternative nanocomposites have been developed to measure benzene and acetone by employing a template-carbonization strategy to generate well-ordered mesostructured silica−carbon nanocomposites. The carbon coating on the silica mesopore surface serves to increase hydrophobicity of the material and reduce the surface effects of humidity. This nanocomposite is very promising for monitoring air quality in the field, because it has a fast response time (2−3 s), recovery time (16−19 s), and is stable over 42 d.[75]

Another common reagent for industrial processes is ammonia (NH_3), which OSHA has set the exposure limit at 100 ppm for individuals throughout a work day. Recently, polyaniline (PANI) and CNT composites have attracted a lot of attention for use as NH_3-sensitive electrode materials. Chen and colleagues, in particular, have focused on various combinations of conductive polymers and CNTs. The group developed an electrode material composed of a transparent CNT film coated with hierarchically nanostructured polyaniline nanorods. The resulting electrode is flexible, selective for NH_3, and has a detection limit of 1−100 ppm.[76] The same group developed a water-enabled healable NH_3 film sensor. The Meyer-rod coating method was employed to coat oxygenated multiwalled CNTs (MWCNTs) onto polyelectrolyte multilayer film (PEM). The healable nature is a result of the lateral movement of the layer-by-layer assembled PEM films, which restore separated areas of the CNT layers. This film provides an improved lifetime via its healable nature while maintaining the selectivity and sensitivity of the original sensor.[77]

Xue et al. have also worked with PANI/CNTs to detect NH_3 gas, opting for a different approach by adding ammonium persulfate before film polymerization. These sensors have fast response and recovery times, flexibility, selectivity, and a low detection limit for NH_3 from 200 ppb to 50 ppm. While each of these materials offers unique benefits, research into developing CNT-based sensors for NH_3 detection is ongoing.[78]

Portable air sensors for security and defense applications are also progressing with the development of a wearable ring sensor to detect nerve agents and explosives. Two carbon-based working electrodes work in parallel using square wave stripping voltammetry (SV) and chronoamperometry for the detection of nitroaromatic and peroxide explosives, respectively. For detection of compounds in the atmosphere, an agarose layer is applied to facilitate diffusion to the carbon surface. Efforts to improve the stability of the agarose layer and thus the lifespan for gas detection are ongoing. Nonetheless, these sensors are extremely promising for wearable gas detection due to their small size and selectivity.[79]

Water. The rise of industrial, agricultural, and pharmaceutical advancements, along with the pervasive nature of contaminants, has threatened natural waters, resulting in widespread effects across trophic levels. This section details the most recent and promising developments in electrochemical sensing of aqueous environments, including, rivers, oceans, freshwater, and tap water. By far, there are more studies of this nature than the other sections in this review, in our opinion, because water sources are easily accessed and are more conducive for electrochemical measurements (ionic strength). Four classes of contaminants commonly found in natural water sources and tap waters are highlighted: heavy metals, industrial pollutants, anthropogenic endocrine disruptors or pharmaceuticals, and agricultural agents.

Metals. Metals, such as Pb, Cd, Hg, and Cu, originate from many sources, including natural sources and industrial and manufacturing effluents. Electrochemistry is capable of determining speciation, which is useful due to metal readiness to change between ligand-bound and "free" or hexa-aqua complexed states. This change of state can occur via minor variations in environmental parameters such as pH; thus, it is highly desirable to preserve the integrity of the sample by making measurements at-source.

Metal measurements are often performed on carbon using SV.[80,81] With the advent of screen-printing technology, carbon electrodes are frequently fashioned into small, disposable probes.[82] Though carbon exhibits excellent electrochemical properties, selectivity is an ongoing challenge for trace metal analysis, because free metal ions are similarly sized and charged. There are few reports within the last three years that utilize nonfunctionalized carbon materials for aqueous metal monitoring.[83−85] Thus, surface modifications, outlined below, are employed to improve sensitivity and selectivity toward target metal analytes and to prevent interferences from small molecules, proteins, and natural organic matter.[86]

Conductive Polymers. Nafion (NA) is a cation exchange polymer, used frequently in sensing applications over many decades. In general NA is applied in conjunction with binding agents, such as dimethylglyoxime (DMG), and ionophores for heightened selectivity.[87−90] Some other conductive polymers have been introduced. Hassan et al. used poly(1,2-diaminoanthraquinone) for multielemental analysis (Cd(II), Hg(II), Pb(II), and Cu(II)) in tap water.[91] Additionally, Pan et al. modified GCEs with polypyrrole/sepiolite nanofibers for Cd(II) and Pb(II) in tap and lake waters.[92] For more detailed information on other conductive polymers that show promise for metal ion sensing, we direct the reader to Deshmukh et al.'s 2018 review, titled Composites Based on Conducting Polymers and Carbon Nanomaterials for Heavy Metal Ion Sensing.[93]

There is growing interest in another class of polymers that are ion imprinted (IIPs) for a target analyte. The function of IIPs is governed by size and charge exclusion, attracting small metal cations, and differing pore size for each analyte. IIPs have been designed for Pb(II), Hg(II), and Ag(I), and applied in tap, river, and ground waters.[94−98] Notably, Sebastian et al. introduced MWCNT/IIPs as both a sorbent and a sensor for Pb(II) and Co(II), as applied to monitoring lake water, mining effluent, and fertilizer.[99,100] Additionally, IIP nanoparticles have been employed to detect Ag(I), Hg(II), and Pb(II).[101−103] While attractive, there is still work to be done to improve the analytical response of IIP-based sensors in the context of temporal resolution (oftentimes more than 15 min of preconcentration is required before analysis).

Chemical Agents. Carbonaceous materials can be combined with other chemical agents that have high affinities for metal ions, including tap, river, and lake water, among others. Nitrogen, sulfur, and oxygen functional groups are frequently used to create composite materials.[104,105] Examples of this include N-doped quantum dots,[106] N,S-codoped porous nanofibers,[107] and carbon nitride nanosheets[87,108,109] that have been designed for multielemental analysis in water sources. Gao et al. improved sensitivity by using metal organic framework templates to create hollow, porous nanofibers, increasing the surface area of the N-doped carbon composite for Pb(II) and Cd(II).[110] Later in 2018, Gao et al. created a combination composite of N,S-codoped porous nanofibers for Cd(II) detection.[107] Additionally, Manna et al. showed that S-doped porous GO exhibits excellent selectivity toward Hg(II) detection over other metal interferences.[111]

Amino acids have been employed because of their high affinities for metal ions. Ramirez et al. and Gutierrez et al. applied cysteine-functionalized SWCNTs for Pb(II) and Cd(II) detection, respectively, in tap, rain, and groundwater samples.[55,112] Additionally, Dalmasso et al. coated GCEs with a polyhistidine/MWCNT composite for Cu(II) detection in rain and tap water samples without any pretreatment.[113] Taking this a step further, Nasir et al. reported a comprehensive study analyzing the electrochemical responses of several amino acids, selecting glycine as the optimized functional group to use. With this method, they are able to achieve multielemental analysis, simultaneously measuring Zn(II), Cd(II), Cu(II), and Hg(II), and apply this method to analyzing spring, river, and industrial waste waters.[114] Likewise, Wang et al. reported an aptamer-functionalized graphite/graphene carbon-nitride nanocomposite for Cd(II) sensing applied to tap, lake, and industrial wastewater.[109]

Some metal analytes are more difficult to measure than others. For example, Ni and Co do not easily preconcentrate, requiring adsorptive stripping voltammetry (AdSV) with a complexing agent. The most common complexing agent is DMG, often immobilized in NA.[88,89] In recent years alternative chelating agents have been proposed. Hussain et al. explored various derivatives of benzenesulfonohydrazide and NA to develop a Co(II) sensor with excellent selectivity over other metal ions.[90] Additionally, Sheikh et al. were able to detect trace amounts of Ni(II) using a novel chelating agent, namely, bidentate N,N′-(ethane-1,2-diyl)bis(3,4-dimethoxybenzenesulfonamide).[115]

Other novel measurement platforms incorporating complexing agents or ionophores offer enhanced selectivity for detecting Pb(II), Cu(II), and Hg(II). These agents are oftentimes immobilized into a polymer composite and drop-casted onto the electrode. One complexing agent, ethylenediaminetetraacetic acid (EDTA), was immobilized onto carbon nitride nanosheets to monitor Pb(II) in surface, tap, mineral, and waste waters.[108] Additionally, Liao et al. utilized NA composites with bis(indolyl)methane/mesoporous carbon nanofiber and salicylaldehyde azine/MWCNTs for Hg(II) and Pb(II), respectively, in river waters.[116,117] Carboimidazole is another interesting ionophore because of imidazole's N-rich structure, which increases affinity toward metal ions in wastewater samples.[118]

Another functionalization approach is to covalently graft an ionophore to the electrode surface. Yang et al. and Fomo et al. used click chemistry to covalently attach ionophores to the electrode surface.[50,119] Yang et al.'s breakthrough study employs ionophore-grafted CFMs coupled with fast-scan cyclic voltammetry (FSCV) for ultraselective Cu(II) detection in the presence of other divalent metals at 10-fold higher concentration. The top panel in Figure 4 illustrates ionophore attachment to the CFM surface. In the bottom panel, color plots and cyclic voltammograms indicate that the rapid adsorption-governed response of fast voltammetry on CFMs is not deterred by the attachment of an ionophore. Furthermore, the LOD (0.3 ppb) is improved in comparison to an unfunctionalized CFM (15.8 ppb).[50,120]

Industrial Pollutants. In industrial processes, durability of materials is desirable; however, this comes at the expense of these materials, when disposed of, not readily degrading. Most efforts for developing industrial waste sensors are directed toward detecting phenolic compounds. Of these, phenolic isomers hydroquinone (HQ) and catechol (CC) are highly stable and toxic. Yi et al. reported a composite polystyrene/poly acrylic acid/GO film that is pH-responsive and able to evaluate HQ with excellent selectivity over other interferences (ascorbic acid, uric acid, and CC).[121] B-Doped graphene has also been employed for simultaneous analysis of CC and HQ,[122] CNTs for CC, p-cresol, and p-nitrophenol,[123] and chitin-stabilized graphite for CC, HQ, & resorcinol[124] in various water sources.

Bisphenol A (BPA) has gained significant attention because of its use in food packaging and plastics and was banned in

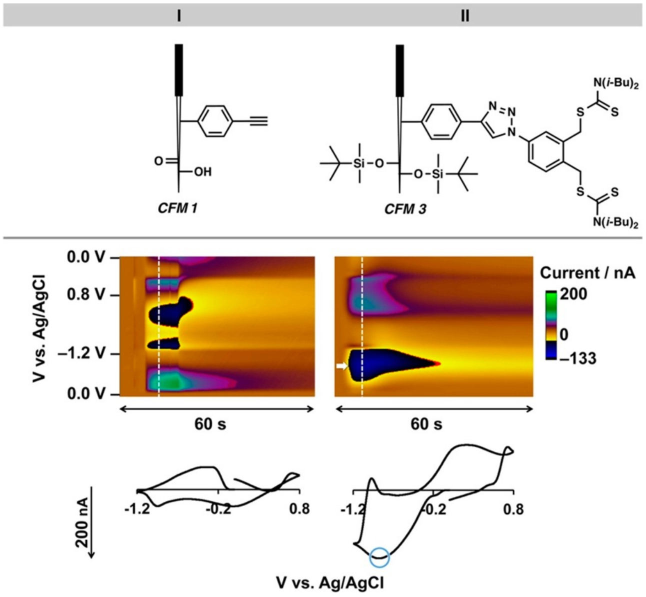

Figure 4. A representative color plot and cyclic voltammogram of 1 uM Cu(II) collected in a mixed metal solution using CFMs (I) before and (II) after covalent functionalization with a Cu(II) specific ionophore. Mixed metals [10 uM]: Zn(II), Cd(II), Ni(II), Co(II), Ca(II), Mg(II), Pb(II), Mn(II). All counterions were NO_3^-. Reproduced from Yang, Y.; Ibrahim, A. A.; Hashemi, P.; Stockdill, J. L. Analytical Chemistry 2016, 88, 6962−6966. Copyright © 2016 American Chemical Society.

2012 after being identified as an endocrine disruptor. Hou et al. developed an electrochemical sensor for BPA using GO nanosheets and incorporating an ionic liquid (n-hexyl-3-methylimidazolium hexafluorophosphate). The high ionic conductivity of this ionic liquid facilitated electron transfer, enhancing sensitivity and long-lasting stability.[125]

A common modifier for analyzing phenolic compounds is β-cyclodextrin (β-CD) because of the selective binding sites within hydrophobic molecular cavities. Zhu et al. utilized β-CD/graphene nanoribbon hybrids to measure o-chlorophenol in river water, reporting a 0.5 ppb LOD.[126] Similarly, Gao et al. used carboxyl-MWCNT/cyclodextrin edge-functionalized graphene composites for detecting 4-aminophenol, 4-chlorophenol, and 4-nitrophenol (4-np) in tap water.[127] Additionally, Yu et al. reported a new nanocomposite material modified with hexadecyltrimethylammonium bromide, carbon dots, and chitosan for an environmentally friendly electrochemical sensing of 2,4-dichlorophenol. The selectivity of this sensor, however, requires improvements in the presence of other phenolic compounds.[128]

Anthropogenic/Pharmaceutical Pollutants. Pharmaceutical agents, such as endocrine disruptors and antibiotics, are often released in the environment from human excretion in wastewater.

Contraceptives and naturally secreted hormones are among the most commonly found endocrine disruptors in water sources. Exposure to endocrine disruptors via drinking water ingestion has been linked to breast and prostate cancers. Dong et al. reported biochar as a unique electrode material with highly efficient adsorption to study a harmful steroid hormone, 17β-estradiol, in groundwater.[129] Rather et al. also determined 17β-estradiol in wastewater with a graphene-amplified aptasensor, showing excellent sensitivity and good selectivity over estrogen and testosterone.[130] Similarly, antibody immobilization is used to measure a common contraceptive compound, ethinyl estradiol, on a paper-based device in river water samples.[131] Estrogenic phenolic compounds have similar structures; thus, Bragga et al. reported a combined quantification of a total of four compounds (estrone, estradiol, ethinyl estradiol, and estriol) with a molecularly imprinted polymer (MIP)-modified rGO electrode. This sensor shows excellent selectivity over HQ and CC and was applied for determination of estrogenic compounds in river water.[132]

Acetaminophen is also found in source waters. Alam et al. used MWCNTs modified with β-CD for simultaneous determination of estrogen and acetaminophen.[133] Another interesting study coupled a CNT-based detector with chemometrics to achieve multicomponent analysis of four phenolic analytes, including HQ, CC, 4-np, and acetaminophen in tap and waste waters.[134]

The anticancer drug flutamide has garnered attention, because water treatment facilities fail to remove it from potable water sources. Kubendhiran et al. used a carbon black/β-CD nanocomposite to measure flutamide and 4-np, which exhibits excellent mechanical stability for four weeks, and applied this sensor to tap water samples.[135] Antibiotics are also finding their way into natural waters. Tetracycline is one commonly administered antibiotic, determined using a unique potato starch and carbon black nanoball sensor in river and tap water.[136] Magnetic MIP nanoparticles are employed to measure another antibiotic, diethylstilbestrol, in lake water.[137]

Agricultural Pollutants. Two classes of agricultural pollutants are found in natural waters: pesticides and fertilizers. Most pesticides function via their actions on the central nervous system and as a consequence can be harmful to humans and animals. Organophosphate pesticides, whose adverse health effects are well-established, are still widely used. Yola et al. applied a unique approach by combining MIPs with carbon nitride nanotubes and graphene quantum dots for measuring chlorpyrifos in waste waters. This method is extremely sensitive, with a 0.7 ppt LOD, and is stable over 45 d.[138] Another organophosphate, diazinon, was quantified using a similar approach employing MIP/CPEs to provide a 700-fold increase in selectivity over interferences.[139] This method by Khadem et al. was also used for dichloran, a chlorinated nitroaniline fungicide.[140] Urbanová et al. were able to achieve multianalyte detection, measuring insecticides thiamethoxam and imidacloprid simultaneously on a GO-based sensor.[141] Herbicides, naptalam,[142] 2-methyl-4-chlorophenoxyacetic acid (MCPA), and its metabolite 4-chloro-2-methylphenol[143] have also been studied using carbon-based electrochemical probes. In the case of MCPA, a PANI/β-CD/MWCNT was used to probe the compound photodegradation over time in real water samples.[143]

As the climate changes, there has been a recent surge in disastrous natural phenomena, such as tropical cyclones that mobilize nutrients and facilitate harmful algal blooms. These blooms are particularly pervasive in shallow waters in the Gulf of Mexico, near the Florida coastline. This phenomenon has gained significant attention in the news for negative effects on marine ecosystems and animal and human health. There has been significant interest in detecting nitrite in the context of these blooms, because it is an important limiting nutrient for plant growth. Polymer-coated GC,[144] N-doped rGO,[145] and acid-functionalized MWCNTs[146] have been reported for nitrite sensing, as well as two other unique probe materials.

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Zhang et al. reported measuring nitrite with bacterial cellulose, offering excellent biocompatibility and mechanical strength, coupled with GO, to electrochemically activate the composite material.[147] Additionally, Yallappa et al. used mesoporous carbon nanospheres recycled from biorenewable arecanut seeds to make measurements in lake and seawater.[148] Another notable study reported a total analysis system, capable of measuring multiple analytes, including nitrate, nitrite, salinity, and chloride, in seawater.[149] Built-in sample pretreatment, acidification, desalination, and in situ calibrations allow this device to make in situ measurements.

Soil and Plants. Certain pollutants, including heavy metals, can persist for years in soil. This is because of the high concentration and diverse binding abilities of dissolved organic matter that stabilize these chemicals. Environmentally disrupting events such as climate change, storms, and agricultural cultivation can mobilize these chemicals. One important example is 2,4,6-trinitrotoluene (TNT), a toxic, explosive agent. A new method for detection of TNT in soil and water has been developed using GCEs modified with carbon nanodots (CDs). A microwave-assisted pyrolysis method combining carbon nanodots and ethylenediamine was used to synthesize nitrogen-rich carbon nanodots. The amine groups on the CDs allow for the detection of TNT, as CDs and TNT form complexes through charge transfer. These electrodes have both a fast response time of 30 s and a wider linear detection range than previous techniques.[150]

Another toxic and persistent pollutant is As. As was previously used as a pesticide, and it is currently used in the metal industry and in antiparasitic drugs for poultry. By far the most common source of As contamination is the mobilization of naturally present As via anthropogenic activities (e.g., fracking).[151] Quantification of one As-based poultry drug, roxarsone, can be easily performed using a carbon paste microelectrode (CPME), providing a more economical alternative to traditional measurements. To prepare the electrodes, Amberlite XAD-4 resin was combined with carbon paste, added to a plastic micropipette tip, and the tip was smoothed. The resin serves to preconcentrate the analyte, as Amberlite XAD-4 has a high selectivity for roxarsone. Overall, the electrode boasts low detection limits, high sensitivity, selectivity, stability, and reproducibility for measuring roxarsone in chicken feed and litter.[152]

Tl, Pb, and Hg are all toxic metal contaminants that can accumulate in soil. A new modified electrode is exploiting graphene's electron-transfer abilities and an ionic liquid binder to improve the electrode's sensitivity. Furthermore, incorporation of a synthetic phosphorus ylide into the matrix of ionic liquid/graphene paste composite allows for simultaneous detection of Tl, Pb, and Hg, metals whose voltammetric peaks overlap when analyzed by other methods. This novel modification proves selective for the three target analytes when compared to 20 other potential interferences and was successfully validated in real soil samples.[153]

Simultaneous detection of heavy metals also has applications in understanding phytoremediation, which was the goal of recent work by Lv et al. The group developed a carbon fiber disk microelectrode by assembling oxygen-functionalized carbon nitride nanosheets onto MWCNTs (Figure 5 bottom left panel). Differential pulse anodic SV (Figure 5 top left panel) along with the carbon disk microelectrode allows for the simultaneous detection of Cu, Pb, and Hg. As shown in the right panel of Figure 5, the microelectrode measures at different points along the root of a rice plant to determine how the plants uptake the three target metals. The development of this technique provides great promise for future on-site ion flux monitoring.[154]

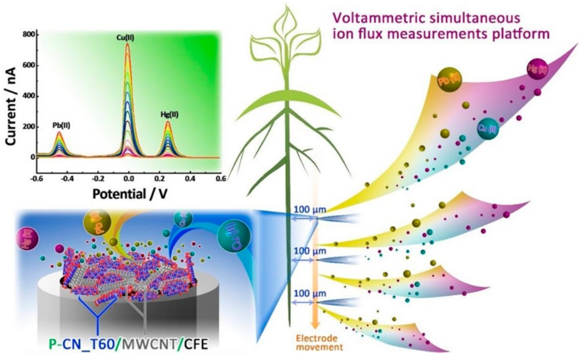

Figure 5. Graphical abstract in which the top left image represents the simultaneous detection of Pb(II), Cu(II), and Hg(II) via SV. The bottom left image visualizes interactions between metal ions and surface modifications on the electrode surface. On the right is a graphical diagram depicting metal ion flux measurements made at different points along the stem of a plant. Reprinted from Lv, H.; Teng, Z.; Wang, S.; Feng, K.; Wang, X.; Wang, C.; Wang, G. Sensors and Actuators B: Chem. 2018, 256, 98−106. Copyright © (2018), with permission from Elsevier.

Food and Drink. Contamination, whether it be from natural sources or anthropogenic, is particularly concerning when it is found in food and drink products, since they pose a high risk of illness. Common contaminants include metals, pesticides, fecal matter, and salmonella. Additionally, adulteration of drinks with date-rape drugs is becoming a growing concern. Each of these applications can greatly benefit from a portable sensor, especially one that can be used by the average consumer.

Mn, while an essential nutrient, can be toxic in high doses and is found in tea and yerba mate products. A carbon SPE was employed with cathodic SV to improve the sensitivity of this portable sensor. For further improvements to sensitivity and reproducibility, 1,4-benzoquinone and 3.5% NaCl are added to the buffer that is used to soak the tea leaves. A detection limit of 30 ppb was achieved, a concentration below the reported Mn values in tea samples. The sensor is selective for Mn over only five of nine potential interfering metals. Nonetheless, this technique successfully measured Mn in yerba mate and green tea samples with accuracy comparable to traditional techniques.[155]

Food-borne illnesses are commonly caused by *E. coli* or salmonella contamination. There is a constant push for better detection methods for these substances. Stencil-printed carbon electrodes were recently used to detect *E. coli* on alfalfa sprouts. Improvements to the electrode sensitivity are currently ongoing. Nonetheless, this disposable sensor provides an attractive low-cost approach for detecting fecal contamination of food products.[156] Likewise, an rGO/MWCNT nanocomposite could prove very useful for measurement of salmonella in chicken samples. The nanocomposites are reproducible and selective for salmonella while also having detection limits below other methods. Significantly, this sensor allows for detection of salmonella on chicken with no pretreatment or extraction.[157]

A disposable sensor has been developed for the detection of date rape drugs in whiskey, which is a complex matrix. This particular sensor is intended for use by forensics teams. The low-cost disposable sensor is made using graphite pencil filling in a preprinted electrochemical cell, which is then laminated and has a Ag ink reference electrode. Overall, the paper-based device has a short lifetime but good reproducibility. The device was successfully used to detect metamizole, paracetamol, and midazolam maleate in whiskey.[158]

Detection of pesticide residue on fruit is especially important for organophosphates, which are considered particularly hazardous as described above. The method of detection for these analytes is commonly via enzyme biosensors. In the development of a "lab-on-a-glove" sensor, carbon still has a role to play. On the thumb finger of the glove a stretchable carbon disk is printed to allow for collection by swiping across a surface. The index finger contains the three-electrode biosensor, and following the collection of the analyte on the thumb, the two fingers are joined together to complete the electrochemical cell, and analysis is performed using a wireless miniaturized, portable potentiostat attached to the back of the hand. Though carbon is not used here as the detection material, its superior adsorption properties make it an ideal material for collecting pesticide residue from food surfaces.[159]

BIOMEDICAL MEASUREMENTS

Physiological systems are complex and dynamic. Biomedical analyte detection must be both rapid and accurate to allow for measurements either ex vivo or in vivo. Ex vivo measurements are often less complex than in vivo when considering the challenges associated with accessibility and immune response of the intact system. To accomplish biomedical measurements, much of the current work employs carbon or carbon-based sensors. These sensor improvements are in healthcare, but not all measurements are restricted to the clinical setting.

POC sensing is accomplished "near or at the site of patient care"; the goal of POC sensors is to integrate the clinic with the lab.[160,161] These sensors are advantageous because they often provide a self-contained, portable, and easy-to-use device for biological analysis. The frontier in biomedical measurements is wearable devices for use anywhere, at any time. Wearables must accomplish both the specificity and accuracy of a benchtop sensor but also include portability and ease-of-use components. In this section, we highlight some of the most advanced uses of carbon-based detection for analyzing biomolecules. These tools can be found via single use/disposable or chronic use/implantable devices. Specifically, we will be covering carbon's use in biological measurements emphasizing a progression toward POC and wearable sensors.

Biological Sensors. Ex Vivo Sensors. Ex vivo analysis is of a sample outside of the body. Although perhaps not as informative as in vivo analysis, ex vivo analysis is extremely desirable, since it is noninvasive. This type of analysis can be used for detection of biological molecules, disease markers, and drug concentrations. Below, the most recent ex vivo carbon detection schemes for biologically relevant molecules, with near-immediate promise for POC analysis, are discussed.

Blood. Blood is straightforward to obtain and is an excellent source of biological information that serves as a good predictor of overall health. There are many analytes that can be detected directly from blood using carbon-based sensors. For example, Dhara et al. developed a nonenzymatic glucose sensor using GO and Pd−Cu oxide nanoparticles in a nanocomposite and drop-cast this composite onto a carbon electrode.[162] This sensor has a high sensitivity and an LOD of 30 nM, allowing it to be used successfully for analysis of human blood serum glucose. In another example, Hughes et al. used an SPE with the electrocatalyst Meldola's Blue as the base transducer to create a disposable biosensor.[163] Here, glutamate dehydrogenase and nicotinamide adenine dinucleotide (cofactor) were encompassed by biopolymer chitosan and MWCNTs and deposited layer-by-layer to allow for amperometric detection of glutamate in blood serum with a 3 μM detection limit and a 2 h lifetime with continuous use.

Another notable blood sensor is for the disease biomarker, HIV-p24 antigen, which can be used for early diagnosis of human immunodeficiency virus (HIV). This antigen has been analyzed via chitosan/MIP/MWCNT-modified GCEs in human serum with excellent LOD (0.083 pg mL^{-1}).[164]

Carbon sensors have also been used for pharmacological analysis in blood samples. For example, sulfanilamide, an antibiotic, can be voltammetrically detected with GCEs polished with alumina, in human blood serum samples, as well as urine, using square-wave SV.[165] This is of particular importance because of increasing antibiotic resistance, making it pertinent to quantify the amount of antibiotics, like sulfanilamide, in human serum.

Urine. Like blood, urine can serve as a window into the body for analysis of biologically relevant molecules, disease biomarkers, and pharmaceuticals. Testosterone can be detected using square-wave AdSV in urine with GCEs.[166] The detection limit for testosterone (1.18 nM) and analysis time is greatly improved with the in situ addition of a cationic surfactant, cetyltrimethylammonium bromide, from which micelles form and encompass testosterone. This sensor does not require sample separation or electrode surface modification, and analysis can be completed in under 5 min.[166] Another molecule of interest, histamine, an important biogenic amine associated with inflammation, can be detected in urine samples. Here, lignin is potentiostatically deposited on GCEs resulting in high sensitivity, high recovery, and a low LOD (0.28 μM) of histamine.[167]

A further study of interest for disease biomarker analysis involves targeting D-Trp, a marker of renal failure, in human urine samples.[168,169] A GO nanoribbon SPE was developed to detect amino acids with enantiomeric resolution as biomarkers of disease. These disposable biosensors use the enzyme D-amino acid oxidase to generate H_2O_2, detected via differential pulse voltammetry, while remaining as a largely portable and fast means for amino acid detection.

Of importance, not only to clinical studies but also to forensics and toxicology, is the detection of pharmaceuticals in urine. Modified GCEs can detect levodopa, a drug that treats Parkinson's disease, and piroxicam, a nonsteroidal anti-inflammatory drug that has been shown to delay levodopa side effects,[170] in human urine.[171] In this study, GCEs were modified with a ZnO-Pd/CNT composite for voltammetric LODs of detections at 0.08 μM levodopa and 0.04 μM piroxicam. Another example is detection of midazolam, a commonly used anxiolytic, using MIP nanoparticles incorporated in CPEs.[172] This sensor is able to detect midazolam in human urine samples with an LOD of 0.18 nM.

Saliva and Breath. Some less-prominent bodily sources for analysis include saliva and breath. Both are noninvasive options for biological analysis. Lee et al. have employed an MWCNT-SPE for a two-part voltammetric detection of homocysteine and glutathione, analytes linked to health conditions like diabetes and cardiovascular disease in synthetic saliva and diluted blood samples.[173] Using a carbon SPE, Garcia et al. employed amperometry to measure α-amylase in saliva, a potential biomarker of neurological disorders with high selectivity, accuracy, and low LOD (1.1 U mL^{-1}).[174] This detection is completed using a sequence of reactions: (1) hydrolysis of α-amylase to maltose and (2) the reduced sugar converts $[Fe(CN)_6]^{3-}$ into $[Fe(CN)_6]^{4-}$ (see Figure 6).

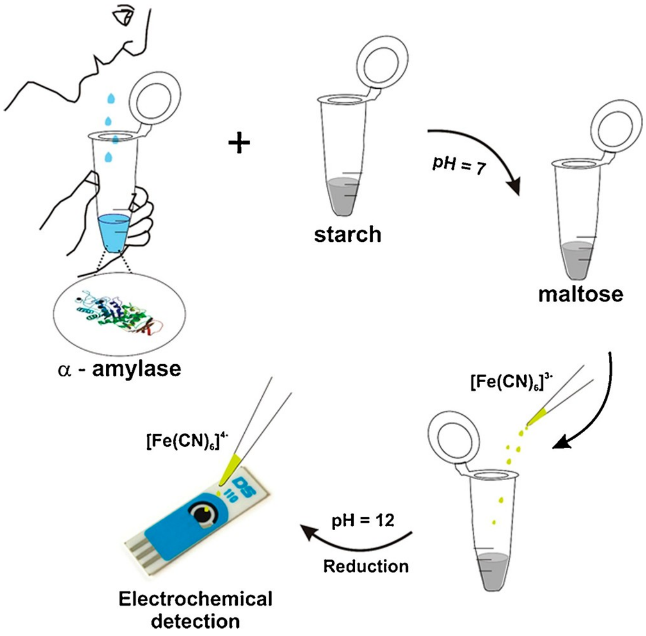

Figure 6. Illustration of the steps involved in the electrochemical measurements of AA. Reprinted from Garcia, P. T.; Guimarães, L. N.; Dias, A. A.; Ulhoa, C. J.; Coltro, W. K. T. Sensors and Actuators B: Chemical 2018, 258, 342−348. Copyright © (2018), with permission from Elsevier.

Breath is an appealing option, as Gholizadeh et al. have developed an rGO fabricated within a polydimethylsiloxane cell on an SPE for nitrate. This portable sensor monitors exhaled breath condensate, in which nitrate serves as a marker of respiratory tract inflammation and asthma.[175]

In Vivo Sensors. While ex vivo analysis is convenient and noninvasive, there are undeniable advantages of making measurements in vivo. Biological systems are rapidly changing, and taking samples for analysis provides only a snapshot of the whole system. Carbon has shown promise in this field and has been used successfully for targeting key organs including the lymph nodes, gut, brain, and skin (described below in wearable sensors) for a wide array of analytes. Examples outlining advances with carbon-based sensors for in vivo sensing will be highlighted herein.

Lymph Nodes. The lymph nodes are an important organ in the immune system with a wide range of biological roles including regulation of the hormone melatonin. Melatonin has long been known for its role in circadian rhythm regulation, but it also participates in anti-inflammatory processes. Using CFMs, Hensley et al. developed a novel detection waveform (600 V s^{-1} scan from 0.2 V to 1.3 V to 0.2 V) to measure melatonin in tissue slices of mouse lymph nodes using FSCV.[176] This method can also codetect serotonin making it a novel and important step toward understanding the modulatory effects of these key molecules on immune responses. Although currently applied to slices, this method shows great promise moving forward for direct in vivo analysis.

Gut. The gut is responsible for processing bodily waste and has been the target of carbon-based sensors. Using a CNT composite array, Patel and colleagues successfully measured serotonin from the entirety of the colon in mice.[177] The group has also utilized a BDD microelectrode for simultaneous amperometric detection of serotonin and melatonin in the colon of a mouse model of inflammatory bowel disease.[178] In zebrafish embryos, Dumitrescu et al. used a CFM electrodeposited with an NO-specific catalytic material, Ni(II) phthalocyanine-tetrasulfonic acid tetrasodium salt, to measure nitric oxide, an important signaling molecule in the intestine.[179] While these sensors are currently limited to animal models, continued advancements will ultimately lead to clinical POC applications.

Brain. The brain remains a particular challenge to access due to the delicate nature of the organ, but CFMs and other carbon-based electrodes have been successfully used for measurements of neurotransmitters and neuromodulators. For this reason, the most recent advancements in neurochemical measurements are first achieved in organism models. In drosophila, CFMs are used to measure serotonin, dopamine, tyramine, and octopamine (of which the latter two serve functions similar to those of epinephrine and norepinephrine in humans) using capillary electrophoresis coupled to FSCV.[180] Rees et al. also measured dopamine, serotonin, and octopamine in drosophila using carbon nanopipette electrodes, which are smaller than CFMs and thus beneficial for in vivo analysis.[181]

In rodents, carbon sensing has been used extensively to study neural activity. Lu et al. described a new porous graphene electrode array for simultaneous sensing and stimulation of brain tissue from the surface without piercing the tissue.[182] This minimally invasive sensor showed high spatiotemporal resolution in analysis of brain activity and precision in electrical stimulation with no degradation over time in rats. Vitale et al. showed that CNT fiber microelectrodes were successful in stimulating and recording neuronal activity in vivo in freely behaving rats for up to four weeks.[183]

The most popular use of carbon-based sensors in the brain is to study dopamine. Dopamine sensing via FSCV is unique in that it can be performed in awake-behaving animals, while fast voltammetric detection of other analytes is currently limited to anesthetized animals.[184] The role of dopamine in health and disease has been studied in a variety of experimental animal models using CFMs. Qi et al. monitored the effects of L-dopa treatment on dopamine neurotransmission.[185] CFMs were also used to simultaneously detect oxygen and dopamine changes during spreading depolarizations associated with brain tissue damage in Sprague−Dawley rats.[186] CFMs can be modified to further improve sensitivity and selectivity and reduce fouling; one notable modification is electropolymerizing DNA and poly(3,4-ethylenedioxythiophene) (PEDOT) polymers onto the electrode surface for dopamine in vivo.[187] Carbon-based sensors have also shown promise for long-term implantation. In nonhuman primates, CFMs were chronically implanted for dopamine measurements over more than 100 d.[188]

In vivo detection of neurotransmitters other than dopamine can be challenging primarily because of structural resemblances and low concentrations of similar analytes. Serotonin has been analyzed using a serotonin specific waveform (1000 V s^{-1}

scanning from 0.2 V to 1 V to −0.1 V to 0.2 V) on CFMs modified with NA for both stimulated release of serotonin via FSCV as well as basal measurements with fast-scan controlled adsorption voltammetry (FSCAV).[189−193] For the latter study, Abdalla et al. employed NA-coated CFMs to measure ambient serotonin in vivo in the hippocampus of mice.[190] In Figure 7 FSCAV color plots (panel A) are presented for in vivo and in vitro serotonin. Panel B displays representative cyclic voltammograms from these color plots that show good agreement, and the inset in panel B is the individual and average serotonin concentrations in the mouse hippocampus. The newest work from this lab is expanding the geographic reach of FSCV to the prefrontal cortex in mice, where discrete serotonin domains were identified by West et al.[193]

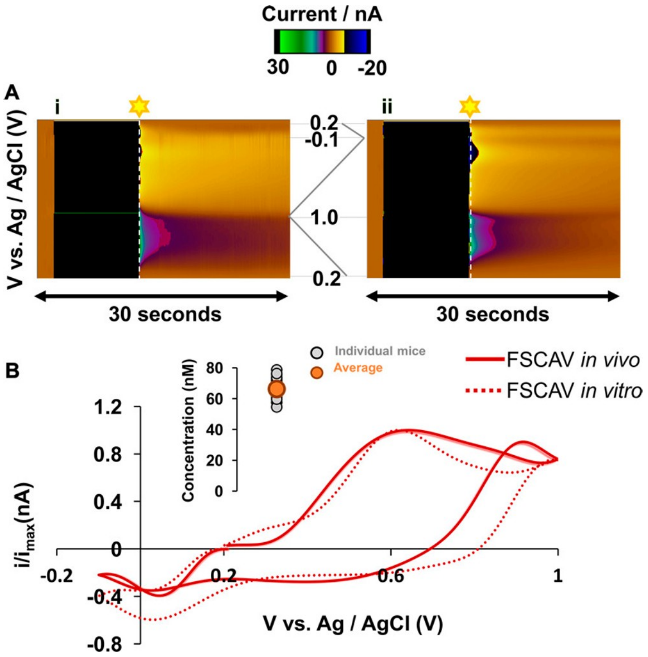

Figure 7. (A) Representative FSCAV color plots of serotonin in vivo (i) and in vitro (ii). (B) CVs extracted from the third scan indicated by vertical dashed lines in A(i) and A(ii). (inset) Ambient serotonin measurements in CA2 region of mouse hippocampus. Gray markers represent individual mice, and orange marker represents weighted averaged response (n = 15 mice ± standard error). Reproduced from Abdalla, A.; Atcherley, C. W.; Pathirathna, P.; Samaranayake, S.; Qiang, B. D.; Pena, E.; Morgan, S. L.; Heien, M. L.; Hashemi, P. Analytical Chemistry 2017, 89, 9703−9711. Copyright © 2017 American Chemical Society.

Histamine has also been evaluated in vivo using FSCV, with NA-coated CFMs and a histamine-specific waveform (600 V s^{-1} scanning from −0.5 V to −0.7 V to 1.1 V to −0.5 V).[194,195] This waveform is unique in that it allows for simultaneous detection of histamine and serotonin in the mouse hypothalamus. Other neurotransmitters and molecules have also been studied with CFMs including norepinephrine,[196] hydrogen peroxide,[197] and adenosine.[198] For more information readers are directed to the recent review by Roberts & Sombers.[199]

Most brain research remains limited to animals; little human work has been accomplished. One example is the application of GCEs that have been fabricated into flexible arrays for use as chemical and electrical sensors as well as electrical stimulators for deep brain stimulation, a potential treatment for Parkinson's disease and others.[200]

Wearable Sensors. With the growing popularity of smartwatches capable of tracking steps, heart rate, and activity type, wearable electronic devices have emerged as a promising detection platform for monitoring human health benchmarks.[201] These devices are easy to use, comfortable, and can be automated, enabling continuous biological sensing.[202] Physical measurements, such as pulse or temperature, made on wearable devices are simple and robust. More elaborate chemical measurements, normally accessed via blood samples, have been performed noninvasively in naturally secreted bodily fluids. These types of measurements are a breakthrough, since they allow automated on-skin analysis (and may eliminate the need for a finger prick or implanted sensor). Continued development and integration of devices like these into daily life will help to better define the human exposome and aid the public health research sector.

Carbon's Roles in Wearable Sensors. Wearable sensors must possess characteristic properties including biocompatibility, flexibility, and comfort to wear on human skin. Graphene and CNTs are frequently employed as base materials, because they can be combined with polymers to create a conductive and stretchable material.[203−208] Conductivity, however, comes at the expense of flexibility: typically a low weight percentage between 2 and 6 wt % CNTs or graphene is added to a polymer composite, due to the loss of flexibility with increased carbon content.[209−214] One study employing CNT/chewing gum sensors notes that there is no change in electrical resistance between 6 and 8 wt % CNT added; however, at 8 wt %, the material becomes much more rigid and loses flexibility.[215] Furthermore, conductivity can also be compromised by the arrangement of CNTs within the material. When adding CNTs to a composite material, aligning the CNTs with the same orientation via a prestretching process has been shown to improve conductivity and electrical performance.[215] As a result of this conductivity/flexibility trade-off, there is much focus on developing novel carbon materials and treatments such as CNT/chewing gum,[215] graphene/silly putty (G-putty),[216] and CNT-wrapped cotton yarn[217] to optimize a balance between conductivity and flexibility. Additional criteria for a wearable sensor are high energy density, load bearing capability, and supercapacitor properties.[218−220] It is cumbersome and inconvenient to connect a power supply to a person; one notable study developed a self-powered material incorporating hybrid piezoelectric-pyroelectric components.[221] This flexible electronic textile demonstrated excellent capabilities for harvesting mechanical and thermal energies, functioning as a nanogenerator.

The vast majority of wearable sensors incorporate these unique materials and deliver two major classes of information, physical and chemical.

Physical Sensing. The large majority of wearable devices collect physical data such as touch,[222−224] movement,[217,225−230] and speech,[231,232] with some sensors capable of measuring electrophysiological signals.[233−235] When the composite material experiences strain, the resistance (R) and fractional resistance change ($\Delta R/R^0$) are measured and reported, generating a calibratable output for each movement. These sensors, typically configured as patches, have been applied on different areas of the body to target physiological responses and vitals. Several studies utilizing sensors attached to the wrist were able to monitor systolic and diastolic blood pressure and pulse.[208,224,236,237] Patches have also been applied to the neck near the larynx, where Park et al. and Wu et al. showed that a wrinkled CNT thin film and carbon black sensors, respectively, are able to differentiate words by means of slight vibrational variations in syllables and intonation.[231,232] Additionally, Boland et al. incorporated graphene into a cross-linked silicone polymer, silly putty, creating what they call G-putty. The utility of this material is depicted in Figure 8, where it is applied to detect finger motion (A), breath (B), pulse (C), and impact from a falling object (D, E), and this material has enough sensitivity to detect a spider walking (F).[216]

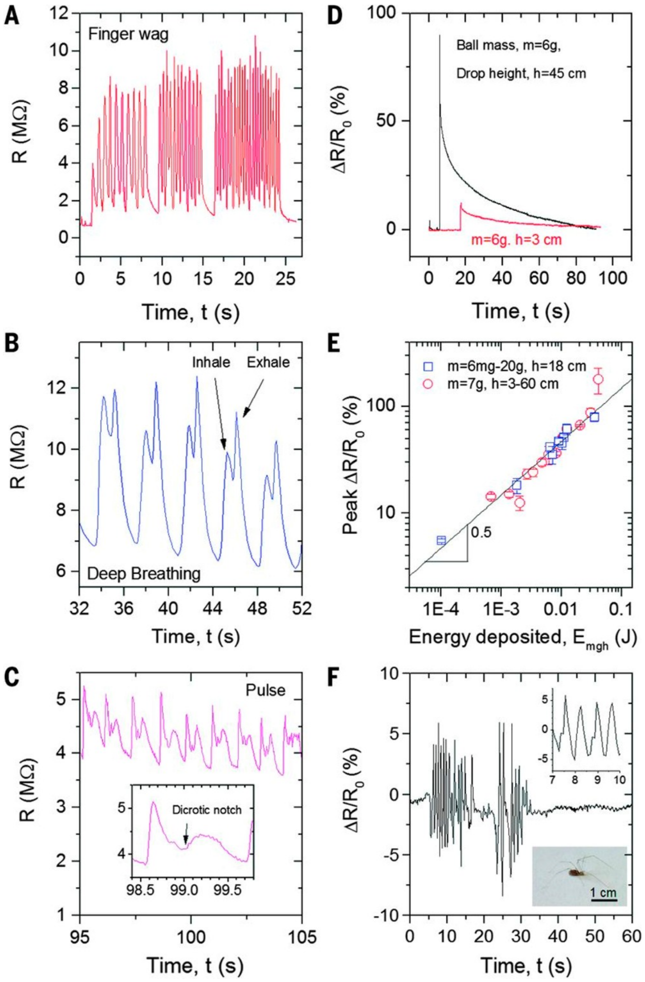

Figure 8. Mechanical sensing applications of G-putty. (A) Finger joint movement. (B) Breathing. (C) Pulse. (D) Falling objects. (E) Energy deposited by the falling object. (F) Spider footsteps (Pholcus phalangioides). From Boland, C. S.; Khan, U.; Ryan, G.; Barwich, S.; Charifou, R.; Harvey, A.; Backes, C.; Li, Z.; Ferreira, M. S.; Mobius, M. E.; Young, R. J.; Coleman, J. N. Science 2016, 354, 1257−1260. Reprinted with permission from AAAS.

These flexible carbon materials are also sensitive to humidity[215] and temperature.[238,239] Dihn et al. in 2016 described the use of CNT yarns, when placed under the nose, to monitor breathing patterns via changes in temperature and humidity, a highly desirable technology for the clinical setting.[240] While these devices offer excellent response time (<100 ms)[240] and good recovery (10s of seconds),[241,242] they are not sensitive enough to detect a change in physiological human temperatures in the absence of exercise.[204]

Ongoing challenges for physical sensing include selectivity, consistent manufacturing quality, and powering. As an example, it is difficult to distinguish between physical parameters such as strain and temperature,[239] while each output is discrete; if both strain and temperature change, the output signal is confounded. The reader is directed to Wang et al.'s and Jian et al.'s 2017 review articles on new carbon-based materials for wearable sensors for additional ongoing challenges. These issues include difficulty manufacturing and pretreating carbon materials in a robust manner, lack of standards or validation methods, and ongoing challenges self-powering such devices while maintaining conductivity and flexibility.[203,204]

Chemical Sensing. Wearable sensors for chemical detection are an emerging field; thus, reports on this type of sensor are limited. Chemical sensing is achieved by selectively detecting analytes in aerosols and bodily fluids. Few analytes have been detected without the use of ion-selective membranes or enzymes. Among these, Lee et al. developed an MWCNT ink-based sensor for potential dopamine detection in sweat, showing excellent selectivity over common interferences of ascorbic acid and uric acid.[243] Additionally, Bariya et al. introduced roll-to-roll gravure carbon-printed sensors, novel for their multielemental versatility. These sensors were capable of detecting caffeine and Cu(II) with SV and a number of other analytes after surface functionalization.[244] Furthermore, wearable sensors have been used to detect gaseous industrial and workplace hazardous.[245] For example, using PANI-anchored MWCNTs, Maity et al. were able to detect NH_3 with good temporal resolution (9 s response/30 s recovery) and high stability (30 d).[246] NO_2 and dinitrotoluene have also been detected with wearable sensors.[247,248]

Enzyme and ion-selective membranes have been utilized to improve sensitivity for chemical sensing. Enzyme-modified graphene- and CNT-based sensors have been incorporated into contact lenses for glucose and lactate measurements in tears.[249−251] Biosensors have been used to measure urea,[252] glucose, and lactate in sweat for real-time health monitoring during exercise and wound healing. Ion-selective coatings on carbon have allowed analysis of perspiration for K^+, Na^+, Ca^{2+}, and pH.[253,254]

The appeal of wearable sensors is that they are user-friendly for a nonexpert. As such, these sensors have been fashioned into a number of different devices, including a smart watch,[253,255] patch,[223,224,226,227,245] fabric,[230,246,254] jewelry,[248] and innovatively, the nosepiece of eyeglasses.[256] Simple, small, and portable voltmeters and potentiostats have been around for many decades and used in proof-of-principle studies for validating wearables utility. More recently, data outputs have been modernized and brought online via integration into an easy-to-use portable sensing platform. As such, many devices are automated with flexible circuit boards and Bluetooth-enabled, so data can be directly uploaded into a user-friendly app on a tablet or smartphone.[234,241,253,257,258]

CONCLUSION

Throughout this review we have highlighted the importance of on-site and POC analysis, emphasizing carbon's use in both environmental and biomedical applications. The criteria for a suitable carbon-based sensor capable of real sample measurements are outlined, including high sensitivity, stability, and reproducibility. Carbon's many advantageous qualities including availability, ease of modification, and biocompatibility make it an attractive material for electrochemical analysis. For environmental analysis, contaminants have been measured in air, soil, water, and consumables. Biologically, studies analyzing various organ systems are detailed both ex vivo, in blood, urine, and saliva, and in vivo, in the lymph nodes, gut, and brain. Special emphasis was placed on studies that show promise for translation to human applications. Finally, wearable sensors were highlighted for applicable on-body monitoring of physical and chemical markers.

The studies mentioned in this review meet many of the criteria mentioned above; however, few successfully fulfill all the criteria necessary for an ideal at-source sensor. As such, there is significant progress being made in the field to improve fast and sensitive detection of contaminants and biomarkers.

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Notes

The authors declare no competing financial interest.

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Parastoo (Parry) Hashemi conducted her undergraduate studies at King's College, London, and received her Ph.D. with Martyn Boutelle in the Department of Bioengineering at Imperial College, London. Her postdoctoral work took place at UNC Chapel Hill with Professor of Chemistry Mark Wightman. Hashemi has pioneered an interdisciplinary and translational research program that centers on biologically and environmentally impactful molecules with applications in point-of-care diagnostics. She has received multiple career awards including: the Masao Horiba Award for Analytical Chemistry (2013); Eli Lilly Young Investigator Award in Analytical Chemistry (2015); a National Science Foundation CAREER Award (2017); the University of South Carolina Breakthrough Stars Award (2018); the Society of Pittsburgh Chemists Pittcon Achievement Award (2018); and the Society of Electroanalytical Chemistry Royce Murray Young Investigator Award in Analytical Chemistry (2018).

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