



FEAST of biosensors: Food, environmental and agricultural sensing technologies (FEAST) in North America

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ABSTRACT

We review the challenges and opportunities for biosensor research in North America aimed to accelerate translational research. We call for platform approaches based on: i) tools that can support interoperability between food, environment and agriculture, ii) open-source tools for analytics, iii) algorithms used for data and information arbitrage, and iv) use-inspired sensor design. We summarize select mobile devices and phone-based biosensors that couple analytical systems with biosensors for improving decision support. Over 100 biosensors developed by labs in North America were analyzed, including lab-based and portable devices. The results of this literature review show that nearly one quarter of the manuscripts focused on fundamental platform development or material characterization. Among the biosensors analyzed for food (post-harvest) or environmental applications, most devices were based on optical transduction (whether a lab assay or portable device). Most biosensors for agricultural applications were based on electrochemical transduction and few utilized a mobile platform. Presently, the FEAST of biosensors has produced a wealth of opportunity but faces a famine of actionable information without a platform for analytics.

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1. A North American perspective on recent biosensor development

A brief literature review was conducted using both Web of Science and SCOPUS, showing that the number of publications in the biosensor area is doubling each decade, a trend that is similar to the global academic field (Van Noorden, 2014). In the last five years the number of publications with the keyword “biosensor” is approximately 5000 peer-reviewed publications per year (see supplemental section for details, Fig S1–S4). During this period, most biosensor manuscripts derived from institutions located in China, followed by the United States, India and a group of countries representing 3–5% of the total publications (South Korea, Iran, Germany, United Kingdom, Japan, Italy, Spain, Canada, and France). Medical applications accounted for approximately 10% of all biosensor publications, followed by applications in food (5%), environmental sciences (3%), and agriculture (2%).

Two key reviews provide a comprehensive summary of the state-of-the-art in analytical biosensor chemistries within food, environmental and agricultural applications. In the area of food (post-harvest) applications, Griesche and Baeumner (2020) show that most devices have focused on detection of food safety pathogens, followed by pesticides, GMO foods, food toxins, food allergens, and chemical residues in food. The critical analysis showed that most biosensor manuscripts address decades-old questions and promise only incremental improvement based on previously successful strategies. Griesche and Baeumner (2020) call for innovations in the four key areas: i) integrated sample preparation, ii) label-free or direct detection in complex matrices, iii) long-term sensor stability, and iv) development of low-cost and user-friendly devices. In environmental biosensor research, Justino et al. (2017) show that most biosensors have targeted pesticides, pathogenic bacteria, heavy metals, organic toxins (e.g., cyanotoxins such as brevetoxin-2), and endocrine disruptors. Justino et al. call for a number of key innovations: i) biosensors which integrate new mobile robotic sensing platforms (e.g., UAV), ii) detailed analysis of complex matrices (e.g., lake, river, seawater, soil and wastewater samples), and iii) development of biosensors which have viable pathways for commercialization. While some of the concepts called for by Griesche and Baeumner (2020) and Justino et al. (2017) overlap (e.g., both reviews called for analysis of complex matrices and integrated sampling), there are concepts which may benefit from convergence of the ideas, in addition to accounting for important advancements in fundamental sensor platform development and data analytics.

The notion of autonomy for cyber-physical systems is a key concept underlying many of the ideas posed in previous biosensor reviews. To date, there is no example or starting point from which to realize the promise of autonomy, or even partial autonomy in the food-environment-agriculture sensor domain. The key to unlocking this toolbox is a concept that has existed for over 20 years, the internet of things (IoT). The location of any particular invention or discovery is not confined by geographical constraints. Given this disclaimer, a detailed summary of the historical context of the realization of IoT at the Massachusetts Institute of Technology, and the milestones that led to this discovery, have been reviewed by (Datta, 2020a). In summary, IoT is a result of convergent thinking in terms of a design metaphor (not a tangible device) that evolved from ubiquitous computing (Weiser, 1991; Weiser et al., 1999). Decreases in the cost of computation and embedding standards such as IPv6 were major milestones between ideation and realization of IoT as we know it now (see review by (Datta, 2020a) for details and specific references). One pivotal tool with access to ubiquitous connectivity between humans and IoT applications is the smartphone (but it is not limited to sensors alone).

In this discussion, we extend the results of seminal reviews by Griesche and Baeumner (2020) and Justino et al. (2017). We call for platform approaches based on: i) use-inspired sensor design, ii) considering the triple bottom line (economic, environmental and social values) in biosensor design, and iii) tools that can support

interoperability (especially between food, environment and agriculture). When synthesized together, this review and the two previous reviews call for eight key actions in the next few decades (see section 8 for discussion).

In the next section, we summarize one platform known as PEAS (percepts, environment, actuators, and sensors), which may serve as the launching pad for biosensor autonomy and decision support. We highlight a few key advancements in the last 5 years that are pertinent to the food, environment, and agriculture biosensing domains.

2. PEAS platform – measure of dynamic performance: optimize and adapt

PEAS is a mnemonic borrowed from agent-based systems and addresses performance through convergence of percepts (P), environment (E), actuators (A), and sensors (S). For additional context of PEAS, see (Datta, 2020a). The PEAS platform is a systems-level approach to data-driven decision support (Datta, 2020b, 2020c) and integrates the operational domain with the cyber-physical domain (Fig. 1). The operational domain is comprised of principal mechanisms relative to the context of the problem, while the cyber-physical domain includes combinations of sensors and actuators with digital feedback loops. The interface between the operational and cyber-physical domains is a dynamic (hidden) layer which interrogates meaningful endpoints (e.g., contextual, technical, economic, social, ecological, feasibility) and initiates new data requirements. In the PEAS platform, data is viewed as a service to society, and the functional products of PEAS are a series of data-driven decision support tools including ART (artificial reasoning tool) and DIDA'S (data-informed decision as a service) (McLamore et al., 2019; Morgan et al., 2020), among others.

Applied to biosensing, the percept (P) component includes features such as sensitivity, limit of detection (LOD), operating range, response time, hysteresis, cost, and perceived usefulness. The environment (E) component includes operational data relevant to land, sea, air and/or water applications. In the actuation (A) component, partial automation (i.e., auto-actuation) of system components may become a complex operation even for a binary process supported by a simple design. Presently, partial-automation has been demonstrated at the lowest level of autonomy (Altintas et al., 2018; Datta, 2020c; Ettenauer et al., 2015; McLamore et al., 2019), where the outcome of sensor data analysis may trigger a low-risk set of linear logic tools to execute a workflow resulting

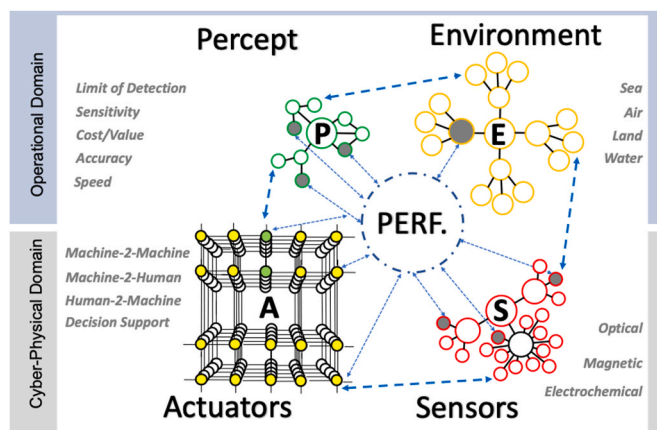


Fig. 1. The PEAS platform for food, environmental, and agricultural technology (FEAST) integrates the operational domain (local environmental situation tied to sensor features) with the cyber-physical domain (combinations of sensors and actuators). As an example, connectivity amongst nodes within the knowledge graph network (dark grey circles) show the convergence toward maximizing QoS. Performance (PERF.) is a result of node convergence in response to a specific need, and varies by application. Individual nodes within the graph network are shown in the supplemental section (Fig S5–S8).

in a decision support tool (e.g., traffic light decision support). Progression beyond simple decision support toward advanced systems (Datta, 2017, 2020b, 2020c, 2020d; McLamore et al., 2019) are extremely challenging. The sensing (S) component in PEAS is based on any combination of the recognition-transduction-acquisition (RTA) triad as described in a number of reviews (Anker et al., 2008; McLamore and Porterfield, 2011; Turner, 2013; Vanegas et al., 2017).

PEAS may be viewed as a horizontal foundation wherever data-informed decisions must combine contextual data with real-time sensor data in one or more analytical engine to generate actionable information. Quality of service (QoS) may be regarded as the key performance indicator for PEAS (see “PERF” in Fig. 1). In this context, the sensor evolves from being a “product” to a conduit for data delivery in the form of sensor-as-a-service. Data fusion and convergence of information are only a part of the data-informed service. The key challenges are to delineate relationships germane to the question, discover relevant data, establish connections, catalyze data fusion, synthesize information, extract actionable information, and deliver a simple command for actuation (execution) or summary of information to a mobile app or device linked to humans in the loop or other higher order decision support systems. In this overview, we have deliberately excluded “comprehend contextual semantics of the query” from this list because of the vast chasm between parsing syntax (using key words to approximately determine, by trial and error, the type of the query) versus actually understanding the semantics. Nevertheless, these processes must be executed in near-real time to deliver a QoS that meets end-user needs if “user friendliness” is desired.

Solutions based on the operational domain or the cyber-physical domain (in isolation) can guide decisions but have major limitations when complex tasks are required. For example, when users (e.g., growers, food consumers, resource managers, policy makers) are integrated into the operational domain, the approach requires several cycles of deconstruction and reconstruction to analyze even the simplest of queries, and often cannot arrive at an unbiased solution. The first step toward resolving a fraction of this bias is contextualization of the problem as demonstrated by transdisciplinary teams. For example, sensory panels are commonly used to provide qualitative indices regarding food and beverage (Alexi et al., 2021) quality, and data may be mined from the published literature for contextualization. While this is a good starting point, in most cases environmental and agricultural problems require a combination of methods for capturing dynamic conditions “on the ground”. For example, the BioNovo group at Universidad del Valle (Colombia), led by Dr. Velez-Torres, established a framework known as CLISAR (closed-loop integration of social action and analytical chemistry research) for integrating local communities into the development of a participatory monitoring program for drinking water (Velez-Torres et al., 2018). CLISAR is a retrosynthetic approach for participatory monitoring and establishes qualitative indices using surveys and behavioral methods (analogous to the sensor panel example), but also includes dynamic characterization using techniques such as social mapping and cogenerative dialogue.

Figure S9 (supplemental section) shows a framework for meaningful information arbitrage within the PEAS domains. This simplified schematic demonstrates a user query made using natural spoken language, initiating a cascade of granular deconstruction. In this example, the lowest common denominator (highest granularity) is the raw data produced by a sensor. User queries are influenced by many factors, including social, political and economic drivers, as well as local environmental conditions and expectations (hence the need for dynamic contextualization). To analyze questions posed by users, natural language processing algorithms within the query layer may be one mechanism to extract word relevance in preformed contexts to inform decision-support tools based on sensor data (see ART, artificial reasoning tools in section 6 and discussion in review by Datta, 2020).

Users can benefit from PEAS as a platform for optimizing performance using sensor data, but there is a myriad of other trans-disciplinary

efforts that are necessary for biosensors (and any other sensor) to contribute societal value, and numerous logistical challenges in terms of implementation (Casalet and Stezano, 2020). In the following sections, we review a few of the key areas needed to develop PEAS for FEAST. First, we summarize the state of the art in biosensor development for the most common recognition-transduction approaches (sections 3–5). Devices are organized based on optical, electrochemical, or magnetic transduction schemes (whole-cell, whole-organism, and tissue-based devices are not reviewed here). We then review advances in portable sensing and discuss advancements in tools for connecting biosensor data to stakeholders via decision support rooted in actionable information (section 6). We note the importance of life cycle analysis and environmental fate of materials (section 7) and conclude by discussing the emerging opportunities and challenges related to the PEAS-FEAST domain (section 8).

3. Optical recognition-transduction schemes

Optical biosensors have significantly advanced in the last decade, from fundamental studies of molecular recognition phenomena to field applications (Unser et al., 2015). Signal (e.g., color, fluorescence, surface plasmon resonance, Raman shift) may be generated directly (type I) via interaction between the target(s) and recognition agent(s); or signal may be generated indirectly (type II) by changes in the optical properties of the environment surrounding the target(s) and recognition agent(s) (Turner, 2013). Some type I methods, such as surface plasmon resonance (SPR) or surface enhanced Raman spectroscopy (SERS) provide label-free detection (Chen and Park, 2018; Chen et al., 2015; Craig et al., 2013; Li and Church, 2014), and are amenable to portable biosensor development. In this section, we summarize progress in optical biosensors within the FEAST domain for three key areas: i) SERS biosensors, ii) phage-based biosensors, iii) SPR film-based biosensors, and iv) nanoparticle-based biosensors. We also discuss recent advancements in material arrangement and architecture for core sensing technology developments.

3.1. SERS biosensors

SERS-based biosensors have attracted significant attention in North America, especially for foodborne/waterborne pathogen detection (see Pilot et al. (2019) for a comprehensive review). SERS biosensors have been developed with a label (improved LOD) or label-free (quicker and easier operation). For example, the Gunasekaran lab at the University of Wisconsin-Madison developed a SERS biosensor integrated with a dielectrophoretic (DEP) microfluidic chip (label assay) using a multiplex strategy (Fig. 2a). The LOD for *E. coli* O157:H7 and *Salmonella* using this approach was 1–10 CFU mL⁻¹ in drinking water (C. Wang et al., 2017). Similarly, the Banerjee lab at Alabama A&M University combined a SERS molecular probe with magnetic-separation (label assay), showing a LOD of 10² CFU mL⁻¹ for *E. coli* O157:H7 in apple juice (Najafi et al. (2014). Since characterization of the molecular origin of bacterial SERS fingerprinting (Ziegler group at Boston University) (Premasiri and Ziegler, 2010) many biosensors have been developed for foodborne/waterborne pathogens. For example, the Irudayaraj group at Purdue University developed SERS fingerprinting techniques to differentiate, detect, and identify *Listeria spp.* and *E. coli* O157:H7 in a variety of food samples (Ren et al., 2020). This rapid, label-free SERS-based approach is useful for high throughput screening of foodborne pathogens with applications in continuous (qualitative) food safety surveillance (Craig et al., 2013). The Irudayaraj group also developed biosensors for mycotoxins using a similar non-invasive approach (Wu et al., 2017).

In addition to assay development, researchers based in North America have also made major contributions to improving SERS efficiency through platform development. For example, the Driskell lab at Illinois State University developed an immunoassay platform that cut the detection time for SERS from 24 h to 10 min (Fig. 2b) (Penn et al.

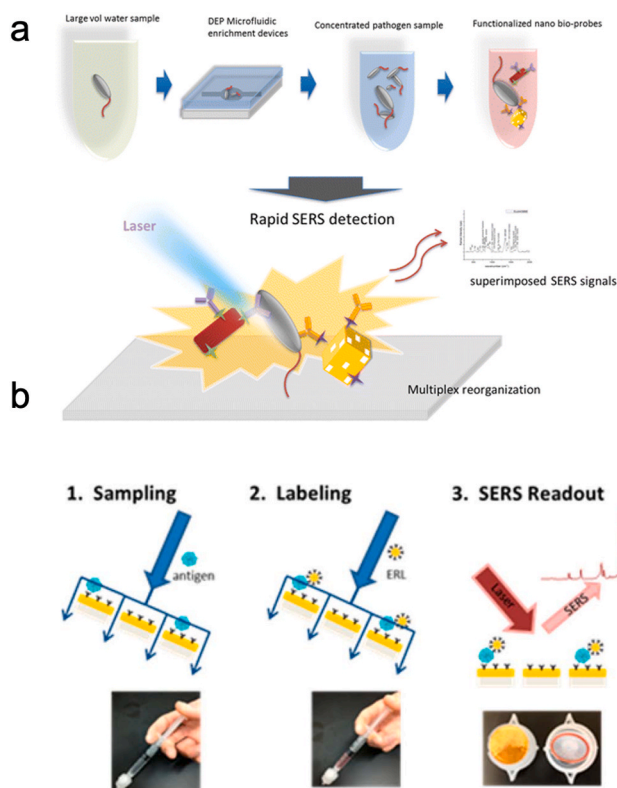


Fig. 2. a) Schematic routine describing the rapid enrichment step using microfluidic device and detection step using the multiplex self-referencing SERS strategy (Wang et al., 2017); reprinted from Datta et al., 2020 with permission from © Elsevier. b) A simple platform for SERS immunoassay (Penn et al., 2013); reprinted from Datta et al. (2020) with permission from © American Chemical Society.

(2013). This approach is anticipated to be a base platform for many future SERS biosensors, overcoming diffusion limitations to accelerate the response time of the immunoassay without use of sophisticated instruments. The Irudayaraj group at Purdue developed a spectroscopy technique that employed rapid Fourier transform for on-site data analysis. This simple method provides accurate *in situ* analysis with low computation demand, lowering the analysis time and enhancing portability of label-free SERS techniques (Yang and Irudayaraj, 2003). Taken together, these two approaches could pave the way for label-free rapid analysis in food samples.

3.2. Phage-based biosensors

One of the latest trends for optical biosensing of bacteria is to use bacteriophages as the recognition element. Upon infection of bacteria by phages, bacterial cells are lysed to release intracellular contents (e.g., endogenous enzymes and other biomarkers) which can “report” the specific biological interaction. One of the most attractive features of using this approach is confirmation of viability. By default, if the phage infects the bacteria, the membrane(s) are intact and the cell is likely viable. Another advantage is that bacteriophage have evolved elegant mechanisms for accessing the bacteria surface, and are less deterred by lipopolysaccharide (LPS) barriers. For example, the Nugen group at Cornell University used this approach for detecting *E. coli* in drinking water (Alcaine et al., 2015; Chen et al., 2015). T7 phage was conjugated to magnetic beads utilized to pre-concentrate *E. coli* in drinking water. Released β -galactosidase was observed as a colorimetric change using the enzymatic substrate chlorophenol Red- β -D-galactopyranoside. A LOD of 10^4 CFU mL⁻¹ viable *E. coli* was achieved within 2.5 h (Fig. 3a). The Bhunia and Applegate labs at Purdue University genetically

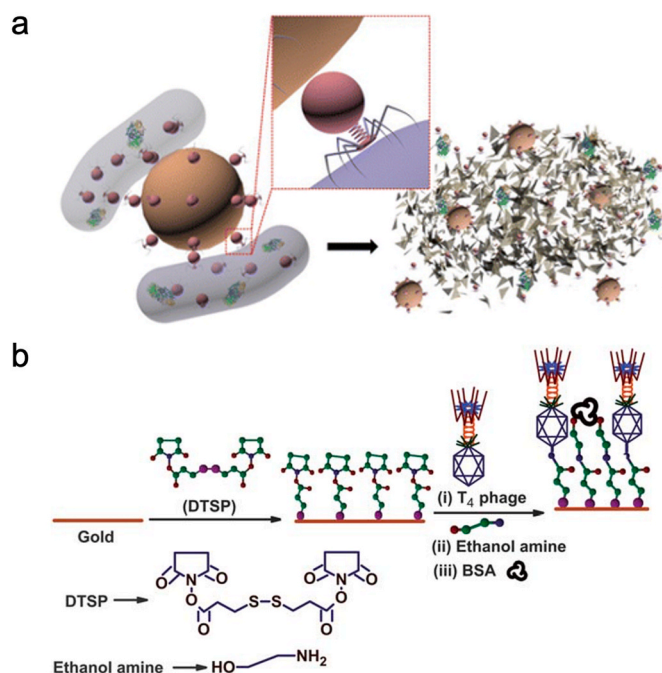


Fig. 3. Phage-based optical biosensor designs for detecting viable bacteria. a) T7-phage conjugated magnetic beads to capture *E. coli* for colorimetric assay; reprinted from Zhang et al. (2016) with permission from © Elsevier. b) T4-phage as recognition agents in SPR detection of *E. coli*; reprinted from Arya et al. (2011) with permission from © Royal Society of Chemistry.

engineering bacteriophages and applied a similar strategy based on enzymatic catalysis based on expression of NanoLuc luciferase (Zhang et al., 2016). This biosensor achieved an LOD of 5 CFU mL⁻¹ viable *E. coli* O157:H7 within 9 h. The Evoy group at the University of Alberta used the T4-phage as a biorecognition agent for a label-free SPR optical biosensor (Fig. 3b). The LOD for viable *E. coli* K12 covered the range of 7×10^2 to 7×10^8 CFU mL⁻¹ (Arya et al., 2011).

In addition to detection of *E. coli*, phage-based biosensors have been developed for *Mycobacterium*, *Salmonella*, *S. aureus*, and *L. monocytogenes* detection in food. Most phage reporters require approximately 24–48 h (including data analytics), and the LOD in real food samples is approximately 10 live bacteria per gram of food (reviewed by Vanegas et al., 2017 and Singh et al., 2013).

3.3. Film-based SPR biosensors

SPR (film-based) biosensors have been developed using glass substrates with thin metal films (typically gold) as the sensing platform. Typically, assays are developed by immobilization of a bioreceptor such as an antibody or aptamer for selective capture (Vanegas et al., 2017). In North America in the last five years, various bacteria detection mechanisms have been developed, including direct label-free detection of intact cells and detection of cytosolic content from lysed cells. For example, the Chen lab at Tennessee State University developed a SPR immunosensor for *Salmonella* Typhimurium for monitoring leafy vegetables. Monoclonal antibodies specific to the flagellin of *S. Typhimurium* were tested in multiple assay formats: direct label-free assay, a two-step sandwich assay, and a one-step sandwich assay with pre-incubation. The LOD for romaine lettuce samples was determined at different levels between 1 and 6 log-CFU g⁻¹ using pre-enriched buffered peptone water and detected well even at the lowest contamination (Bhandari et al., 2019). In a similar project, the Evoy lab at the University of Alberta developed SPR biosensors for analysis of food contaminated with *Salmonella* Typhimurium (LOD = 10^3 CFU mL⁻¹) (Singh et al., 2010).

Beyond bacteria, SPR biosensors have also been developed for

detection of fungal pathogens. The Rodriguez-Delgado group at Universidad Autónoma de Nuevo León developed a SPR biosensor for detection of black Sigatoka disease in banana plantations (Luna-Moreno et al., 2019). The gold thin film immunosensor was based on immobilization of polyclonal antibody that targeted a wall protein (HF1) on the hemibiotrophic fungus *Pseudocercospora fijiensis*. The LOD was $11.7 \mu\text{g mL}^{-1}$, and the operational range was as high as $122 \mu\text{g mL}^{-1}$ for analysis of leaf banana extracts. This SPR immunosensor is the first of its kind for disease surveillance related to *P. fijiensis* in banana groves.

Detection of protein and gene markers is also possible with film-based SPR. The Cheng group at the University of California Riverside developed a highly sensitive SPR method for the determination of *Salmonella* using a DNA hybridization transduction mechanism. A sandwich format was developed by integrating an avidin-linked aptamer used for signal amplification and an aptamer targeting *invA* gene as the target probe. The LOD toward live *Salmonella* was 60 CFU mL^{-1} (P. Lei et al., 2015). Film-based systems have also been used for protein detection. The Lefebvre lab at the Northwest Fisheries Science Center at the National Oceanic and Atmospheric Administration utilized film-based SPR to detect biomarkers (antibodies) linked to amnesic shellfish poisoning in human blood and urine. The SPR biosensor was superior to an ELISA assay for detecting the antibody biomarker, showing higher specificity, use of smaller sample volumes, and incorporation of multiple tests per sample (Lefebvre et al., 2019).

Film-based SPR biosensors have also been developed for a variety of food allergens (Gaudin, 2019), mycotoxins (Ngundi et al., 2006), and environmental pathogens (Marusov et al., 2012).

3.4. Nanoparticle-based SPR biosensors

Localized SPR (LSPR) biosensors have been developed for a number of FEAST applications. As shown in Fig. 4a, there are two common approaches for signal amplification in LSPR biosensors using colorimetric transduction: 1) growth of magnetic nanoparticles (NPs), and 2) shift in LSPR peak associated with aggregation of NPs. The latter mechanism is the most widely employed biosensing scheme, with LSPR peak shift based on aggregation of gold NPs or silver NPs. As observed in Fig. 4b, while the color of stable AuNPs solution is red, the color of aggregated AuNPs solution is purple (Sanromán-Iglesias et al., 2015), and consequently the peak absorbance redshifts. Several naked eye biosensors employing AuNPs have been developed for the detection of food- and water-borne pathogens, and also for indicators of local environmental conditions such as temperature (see reviews by (Azzazy et al., 2011; Bunz and Rotello, 2010; Chen and Gu, 2019; Hahn et al., 2017; Saha et al., 2012; Tallury et al., 2010; Upadhyayula, 2012; You et al., 2018); (Azzazy et al., 2011; Bunz and Rotello, 2010; Chen and Gu, 2019; Hahn et al., 2017; Saha et al., 2012; Tallury et al., 2010; Upadhyayula, 2012; You et al., 2018); (Azzazy et al., 2011; Bunz and Rotello, 2010; Chen and

Gu, 2019; Hahn et al., 2017; Saha et al., 2012; Tallury et al., 2010; Upadhyayula, 2012; You et al., 2018). For example, the Yu group at Iowa State University developed a biosensor based on NP growth as a nano thermal history indicator, which is a viable alternative for the popular time-temperature indicator. This LSPR device was used to monitor temperature abuse in food and biological materials (Wang et al., 2015; Y.-C. Wang et al., 2017), which is critical for supply chain monitoring.

In some cases, signal enhancement is necessary for improving the signal-to-noise ratio when applying LSPR biosensors in complex media such as food samples (Lim et al., 2012; You et al., 2020). Along these lines, the Gunasekaran group at the University of Wisconsin-Madison developed a SPR signal enhancing strategy by using switchable linkers (SL), which are designed to bridge NPs in the presence of target bacteria in a controllable manner (Gunasekaran and Lim, 2018; Hahn et al., 2017; Lim et al., 2012; You et al., 2018, 2020). The LOD for this functionalized NP-SLs biosensor toward *E. coli* was 1 CFU mL^{-1} based on quantitative visible detection of live bacteria in real matrices within ~30 min. In another example, the Neethirajan group at the University of Guelph developed a variety of LSPR devices based on NP aggregation, including immunochromatographic assays for detection of biomarkers in animal agriculture (Ragavan et al., 2018a; Weng et al., 2018), parasites causing diseases such as malaria (Ragavan et al., 2018b), and coronaviruses causing influenza (Ahmed et al., 2018).

Concluding this section, we briefly highlight recent advances in core sensing technologies related to material arrangement and sensor architecture for optical biosensors.

4. Material arrangement and architecture

In the last five years, many labs have focused on improving fabrication procedures with the aim of enhancing optical biosensor performance. Techniques such as SPR (and LSPR) are highly dependent on precise control over material deposition and arrangement. Recent reviews discuss specific interactions of photons with metal films (see review by (Kasani et al., 2019) and nanoparticles (see review (Noguez, 2007) for SPR sensing, which is the core of the observed transduction. Briefly stated, the arrangement and architecture of the material dictate the physics of the photon interactions, and thus the biosensor efficacy. Research in material arrangement and architecture within this context are discussed below, and development of biodegradable sensor platforms for optical biosensing are highlighted.

The Kagan lab at the University of Pennsylvania developed new techniques for patterning sub- $5 \mu\text{m}$ colloidal nanocrystals for application in film-based SPR (Keller et al., 2020). Innovations in colloidal lithography for patterning substrates at the micron scale are critical for realizing the potential of SPR in field measurements within the FEAST domain. In addition, the Kagan lab has also pioneered numerous methods for controlling SPR properties of colloidal nanocrystal assemblies using techniques such as ligand hybridization (Chen et al., 2019). Together, these advances represent new strategies to tune materials for biosensing applications of important targets, including ions, sugars and hormones.

The Schatz lab at Northwestern University has developed numerous devices based on LSPR (Oh et al., 2019). The key SPR feature is the presence of nanoholes or nanostructures associated with the metal film (McMahon et al., 2011). Similarly, the Brolo lab at the University of Victoria developed plasmonic sensors based on periodic patterning of nanohole arrays for analysis of DNA fragments, small molecules, and allergens, amongst other targets (Brolo, 2012). The Brolo group developed a number of low-cost SPR sensor platforms such as plastics and thin film polymers that are coupled with low-cost LED light sources and photodiodes. The innovation of this patterned nanohole array is the utilization of Fano resonance, a phenomenon rooted in the coherent interference between evanescent and propagating modes (Valsecchi and Brolo, 2013). As another example, the Que lab at Iowa State University

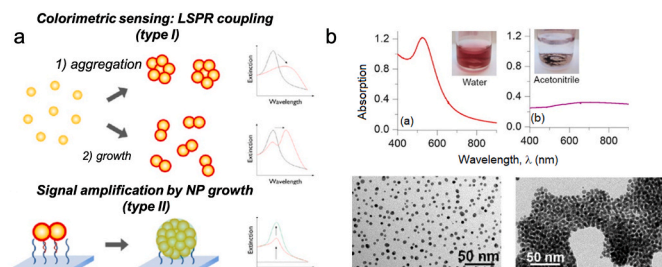


Fig. 4. a) Illustration of two common strategies for visible sensing: 1) via aggregation of NPs (top) and 2) via growth of NPs; reprinted from Guo et al. (2015) with permission from © Elsevier. b) UV-VIS spectrum and TEM image of AuNPs in water and aggregated in acetonitrile; reprinted from Sanromán-Iglesias et al., 2020 with permission from © American Chemical Society.

developed a nanostructured porous array using top-down fabrication processes on aluminum (Che et al., 2015), and demonstrated micro-patterning of molecular beacons for fluorescent biosensing.

Periodicity is indeed a critical feature of SPR biosensors, but fractality is an emerging principle that has recently gained attention. Self-similar (fractal) structures have been used in a variety of LSPR sensors, including suspensions and surface coatings (reviewed by (McLamore et al., 2016)). For example, the Fainman lab at the University of California San Diego patterned fractal structures on nickel-coated borosilicate glass, including Sierpinski geometries composed of biotin (Smolyaninov and Fainman, 2017). Patterning bioreceptors into fractal arrangements may extend the active sensing range beyond the 2 μm limit, which currently limits SPR, potentially even extending into the spatial region relevant to infrared spectroscopy.

4.1. Biodegradable platforms and emerging issues

Biodegradable/biocompatible optical biosensor platforms are important when considering applications in the FEAST domain. The Wan group at the University of British Columbia developed an electrospun nanofiber membrane using the biodegradable polymer poly (aspartic acid) (PASP) for naked eye detection of Cu^{2+} and Fe^{3+} in drinking water based on colorimetric transduction. The LOD for Cu^{2+} was 0.3 mg L^{-1} , and the LOD for Fe^{3+} was 0.1 mg L^{-1} . The sensor was reusable after metal ion extraction by the desorption process for a limited number of hysteresis cycles (Zhang et al., 2019). In another example, the McLamore group at Clemson developed a biodegradable cellulose film doped with anthocyanin extracted from purple cabbage. The material was inkjet-printed and was able to function as a rapid pH sensor across the range of pH 2 to pH 12 (Demirbas et al., 2018), and also demonstrating use as a solar cell for self-powered applications. The Kokini lab at Purdue University developed a SERS biosensor for the peanut allergen protein, Ara h based on a zein film (biopolymer from corn protein). The film was intercalated with gold nanopyramid structures and monoclonal antibodies. Principal component analysis (PCA) was used for creating a sensor with an LOD of 0.14 mg mL^{-1} (Gezer et al., 2016). The Yun lab at Harvard University developed strain-sensitive hydrogel optical fibers which have demonstrated promise as a sensing platform in medical sensing (Guo et al., 2016) but have not yet been tested in FEAST applications. Outside of North America, numerous groups have worked on development of optical biosensors using chitosan as the base material (Rovina et al., 2020; Wongniramaikul et al., 2018). Another innovative platform that has not yet been used for sensing is the bacteria waveguides first developed in China but gaining popularity in other regions (Bezryadina et al., 2017).

Optical biosensors are one of the most promising transduction techniques for label-free detection of pathogens without addition of exogenous reagents. Key targets in the last decade include pathogenic bacteria (*E. coli* O157:H7, *Salmonella*, *Listeria monocytogenes*), viruses (plum pox virus, citrus tristeza virus, potato leafroll virus, and rice tungro bacilliform virus), and mycotoxins. Optical biosensors have been validated in drinking water, apple juice, river water, and lake/pond water (in addition to thin films relevant to food packaging). The main challenges are: i) lack of enhanced control over dielectric effects from SERS substrate to improve consistency, ii) need for sample preprocessing standards within SERS workflow, and iii) lack of easily accessible database of reference spectra for common foodborne pathogens.

In the next section, we summarize recent advancements in recognition-transduction schemes based on electrochemical techniques.

5. Electrochemical recognition-transduction schemes

Several reviews summarize first principles and classic techniques for electrochemical biosensing (Liu et al., 2012; Ronkainen et al., 2010; Wang, 2005). Similar to optical devices, electrochemical biosensors may be classified into label assays and label-free assays, with the additional

feature of identifying whether a redox probe and supporting electrolyte are included in the testing medium (classifying the measurement as Faradaic or non-Faradaic). Non-Faradaic approaches are emerging, but are difficult to analyze in complex matrices. One generic advantage of electrochemical transduction over optical transduction is that opaque samples may be analyzed. In this section, we summarize recent progress in electrochemical FEAST biosensing for i) bacteria detection, and ii) small molecule detection. We also discuss recent advancements in electrode arrangement and material architecture for core sensing technology developments.

5.1. Electrochemical biosensing for bacteria detection

In the last five years, several electrochemical biosensors have been developed for foodborne pathogen measurement, primarily focusing on *E. coli*, *Listeria monocytogenes*, *Salmonella*, *Staphylococcus aureus*, and *Bacillus subtilis*. Most impedimetric immune-biosensors were developed for biorecognition of extracellular structures on target bacteria. The biggest issue in accurate detection of intact bacteria is access to the cell-surface target. The bacteria surface is covered in LPS which is a highly dynamic barrier that “protects” surface protein antigens. Label-free assays which can selectively target intact bacteria are highly desired, as this approach promises detection and also possible determination of cell viability.

The Gomes group at Iowa State University developed an impedimetric biosensor based on laser-inscribed graphene for detection of *Salmonella enterica* in food samples (Fig. 5a). Antibodies were immobilized on graphene electrodes using classic EDC-NHS chemistry and blocking agents were added to limit non-specific binding. The LOD was 13 CFU mL^{-1} , with a response time of approximately 20 min and range of 25–10⁵ CFU mL^{-1} in chicken broth (Soares et al., 2020). In addition, the Gomes and McLamore groups developed nanobrush biosensors for bacteria capture based on hybrid stimulus-response materials. The nanobrushes were immobilized on graphene electrodes, and then bioreceptors (aptamers, antibodies, lectins) were conjugated to the terminal chain for specific capture. The use of nanobrushes allows controlled actuation of the bioreceptor for active capture. For example, *Listeria* biosensors using aptamers as the biorecognition element are shown in Fig. 5b. Extension of the nanobrushes by chemo-actuation improves capture, and subsequent (engineered) collapse improves signal-to-noise ratio. These nanobrush biosensors were also demonstrated on Pt/Ir disc electrodes for detection of *Listeria* in vegetable broth (Hills et al., 2018) and platinum interdigitated microelectrodes for in-pipe detection of *Listeria* in hydroponic water for Romaine lettuce (Sidhu et al., 2020). Regardless of form factor, the LOD for *Listeria* detection was 10 CFU mL^{-1} in complex media and the response time was less than 20 min (10–10⁷ CFU mL^{-1} operating range). To demonstrate the full potential of actuating materials in biosensing (Giacobassi et al., 2021),

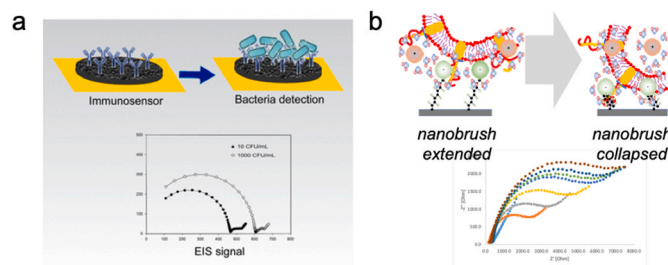


Fig. 5. Biosensors for targeting extracellular targets on bacteria pathogens relevant to food and environmental monitoring. **a)** Immunosenor for detection of *Salmonella enterica* by Soares et al. (2020). Reproduced with permission from © American Chemical Society. **b)** Nanobrush biosensors for *Listeria* based on stimulus-response polymers with aptamers and Ab from Hills et al. (2018) and Sidhu et al. (2020) allow biosensors to be “activated” (extended) or “queued” (collapsed) on demand; image reproduced with permission from MDPI.

demonstrated a partially automated biosensing system where the nanobrush actuation is controlled from a smartphone (see section 7 for details).

Beyond detection, the Mulchandani group at the University of California Riverside developed biosensors for the detection of live/viable *Bacillus subtilis* based on the response of the conductive polymer 4-(3-pyrrolyl) butyric acid to glucose-induced metabolites with a detection range of 6.0×10^3 to 9.2×10^7 CFU mL⁻¹ (Saucedo et al., 2019; Vanegas et al., 2017). Though not discussed in detail here, the ability to determine bacteria viability is crucial in pathogen sensing, and to date there are no robust techniques which can provide this feature in numerous sensing modalities. Rapid, label-free discrimination of viable versus non-viable bacteria is a feature which would be truly transformative in the area of electrochemical biosensing.

5.2. Electrochemical biosensing for small molecule detection

Numerous biosensors were developed in the last 5 years for detection of ions, organic molecules and agrochemicals in FEAST applications. Select examples are highlighted below.

The Claussen lab at Iowa State University developed an ionophore-based electrode for detection of nitrogen in soil (Fig. 6a) (Garland et al. (2018)). Flexible carbon electrodes (laser inscribed graphene) were fabricated using a lithography-free approach and then bacteria-derived macroretrograde ionophore was immobilized on the surface to impart selectivity. The biosensor displayed Nernstian sensitivity with an LOD of 28 μ M and low long-term drift (0.93 mV h⁻¹) in soil slurries. Biosensors have also been developed in the last 5 years for targeting heavy metals in drinking water (Abdelbasir et al., 2018) and key performance indicators of wastewater treatment plant performance (McLamore et al., 2020) using a similar approach.

The Vanegas lab at Clemson University (Vanegas et al., 2018) developed an enzymatic biosensor based on laser-inscribed graphene by incorporating enzyme into a copper/polymer nanohybrid structure used for detecting spoilage indicators/toxins in fermented fish (Fig. 6b). The LOD was 12 μ M and the response time was less than 20 s in fish samples. For analysis of fruit, the Ramasamy lab at the University of Georgia developed a number of biosensors for measuring plant volatile organics as indicators of biotic stress (e.g., phytochemicals, fungi, phytovirus infection). For example, tyrosinase was adsorbed onto carbon nanotube-coated screen-printed electrodes for detection of p-ethylphenol release from strawberries (Fang and Ramasamy, 2016). The LOD was 0.10 μ M and the response time was 30 s for fresh fruit samples. The McLamore and Vanegas labs at Clemson University developed a copper-carbon hybrid biosensor for detection of human urine biomarkers associated with illegal gold mining and use of mercury (Abdelbasir et al., 2018). Copper was extracted from electronic waste and synthesized into copper oxide NPs before adsorption of bio-recognition agents. The use of recovered materials (e.g., electronic

waste, industrial wastewater) is an emerging trend in biosensing (Abdelbasir et al., 2020).

Numerous pesticide biosensors have been developed based on enzyme inhibition using either acetylcholine esterase (AChE) and butyrylcholinesterase. In addition to these classic techniques, other recognition materials are emerging (see review by Pundir and Chauhan, 2012). For example, chemistries based on activity of organophosphorus hydrolase (specific for organophosphates), tyrosinase (specific for atrazine; (Tortolini et al., 2016), alkaline phosphatase (specific for 2, 4-dichlorophenoxy acetic acid; (Bollella et al., 2016), horseradish peroxidase (specific for glyphosate; (Q. Zhang et al., 2015), and methyl parathion-degrading enzymes (specific for methyl parathion (Ye et al., 2016); are emerging. In some cases, multiple enzymes are used to promote synergism and improve accuracy. The Claussen labs at Iowa State University developed nanoporous gold leaf electrodes as adhesive pesticide biosensors based on acetylcholine esterase (AChE) inhibition. The biosensors were selective towards paraoxon (an organophosphate) in soil samples with a LOD of 0.53 μ M and operating range up to 10 μ M in a custom flow cell for sample preparation (A. Hondred et al., 2020). The Lei lab at University of Connecticut developed a nanocomposite of elastin-like-polypeptide (ELP) and organophosphate hydrolase (OPH) doped with titanium dioxide nanofibers and carbon nanotubes (Bao et al., 2016). The ELP-OPH hybrid material was purified from genetically engineered *E. coli* and coated on glassy carbon electrodes. The LOD for organophosphorus pesticides (methyl parathion and p-nitrophenol) was 12 nM and 10 nM, respectively. The biosensor was tested in lake water samples and showed reproducible and reusable detection. Reusability for the ELP-OPH sensor is a major advantage over traditional AChE inhibition sensors, which are single-use devices. In other non-AChE biosensors, the Claussen lab also made numerous innovations in the use of phosphotriesterase trimer (PTE3) for detection of p-nitrophenol. PTE3 was labeled with AuNPs and selective binding was monitored using a multiplexing (self-referencing) approach that compared activity of unbound PTE3 to PTE3-AuNP bioconjugates (Hondred et al., 2017). PTE biosensors (full his-tagged protein) were also tested for detection of paraoxon in water, with a LOD of 3 nM and longevity of approximately 8 weeks (Hondred et al., 2018). The relatively poor selectivity of nearly all biosensor approaches (particularly when multiple pesticides are present) is a major problem and to date few, if any, approaches have been successful. In an attempt to improve performance in mixtures, the Muñoz lab at Centro de Instituto Politécnico Nacional (México) developed a machine learning tool for analysis of multiple pesticides using an AChE biosensor. Use of the artificial neural network improved accuracy and demonstrated the ability to discriminate between chlorpyrifos-oxon, chlorfenvinphos and azinphos-methyl oxon mixtures (Alonso et al., 2012).

Due to the relatively slow progress in enzymatic electrochemical biosensors, many groups have recently shifted focus toward direct electron transfer (DET) facilitated by nanoparticles. Approximately 10% of the publications on enzyme biosensors in North America within the last decade focused on, or mentioned, DET. For example, the Ramasamy lab at University of Georgia developed a bi-enzyme electrode with DET between peroxidase and the graphene electrode for detection of methyl salicylate as an indicator of crop infestation (Fang et al., 2016). In another example, the Krishnan group at Universidad Nacional Autónoma de México developed biosensors based on DET using glucose oxidase (GOx) covalently tethered to chitosan (Krishnan et al., 2017; Kumar-Krishnan et al., 2017, 2016). Various inorganic substrates were used, including Pd@Pt core-shell nanocubes and silver nanowires. Rational genetic engineering for enzyme(s) that favor DET appears to have been absent from research on DET in North America in the last five years, but is an emerging topic.

In the next section, we briefly highlight recent advances in core sensing technologies related to material arrangement and architecture that may have application in electrochemical biosensing over the next decade.

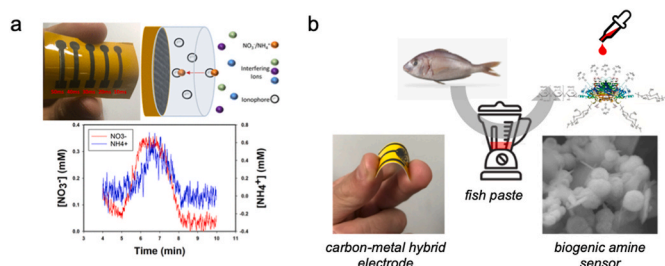


Fig. 6. Flexible carbon electrodes for biosensing environmental and agricultural targets. **a)** Macrotetrograde-based biosensor for soil nitrogen developed by Garland et al. (2018); reprinted with permission from American Chemical Society. **b)** Enzymatic sensor for monitoring biogenic amines in fermented fish and fish paste by Vanegas et al. (2018); reprinted with permission from MDPI.

5.3. Electrode arrangement and material architecture

Many modern electrodes for biosensing are fabricated in-house, using various top-down and bottom-up fabrication techniques. The recent availability of these fabrication methods has expanded the scope of traditional electrochemical biosensor research laboratories, allowing many groups to focus on electrode arrangement and material architecture, including development of biodegradable electrodes. For example, the Claussen lab at Iowa State University developed an aerosol jet printing (AJP) technique and demonstrated the ability to produce high-resolution ($\sim 40\ \mu\text{m}$ line width) interdigitated electrodes (IDE) on flexible substrates. The group in collaboration with Gomes lab at Iowa State University and Hersam lab in Northwestern University also demonstrated application in the FEAST domain by developing allergen (histamine) biosensors functionalized with antibodies for analysis in fish broth (Parate et al., 2020). The printed IDE on flexible substrate has shown a number of applications beyond allergen detection, including wearable sensor applications (Kucherenko et al., 2020). The Claussen lab has developed numerous other relevant techniques for biosensor fabrication such as solution-phase graphene printing (Hondred et al., 2018) and inkjet maskless lithography (Hondred et al., 2017), among others.

For impedimetric sensing, two-electrode symmetrical arrangements such as the classic IDE have relatively high output signal due to the large electroactive surface area taken together with the sinusoidal character of perturbation voltage (Ding et al., 2016; L. Wang et al., 2017). The Li group at the University of Arkansas developed asymmetric electrode arrangements (Fig. 7a) that showed high current density compared to standard comb finger electrodes (Xu et al., 2016). The Gao lab at Reed College, among others, developed IDE with interlocking nano-wires (Fig. 7b) modified with molecular probes have increased surface-to-volume ratio, high sensitivity due to high current density, and in some cases enhanced selectivity due to Kelvin-like effect (Feng et al., 2020; Kim et al., 2016; Li et al., 2017). Wire-based electrodes traditionally have low conductivity, which makes them poorly suitable for electrochemical sensing applications in complex mixtures. The Bai lab at the University at Albany-SUNY developed hexahedral electrodes that significantly extend the application range of wire-based biosensors

(Dong et al., 2019), demonstrating the importance of electrode arrangement. The Javanmard lab at Rutgers University demonstrated true 3D co-planar electrode configurations (Fig. 7c) for in-body monitoring (Mahmoodi et al., 2020), and this geometry could be used for label-free biosensing in packaging and other FEAST applications.

5.4. Biodegradable electrodes and emerging issues

Development of biodegradable electrochemical biosensors is an area of high innovation that is pivotal to sustainable technologies within the FEAST domain. Non-woven porous flexible electrodes have been developed using a variety of techniques. For example, the Stanciu lab at Purdue University developed a biodegradable biosensor for measuring a food protein (gliadin) linked to chronic problems in consumers with celiac conditions. The electrode was fabricated by creating a zein film doped with various conductive materials, including carbon nanotubes (CNT). In a comparative study, zein-CNT hybrid films were better electrodes than zein-graphene oxide or zein-laponite electrodes. The Yadavalli lab at Virginia Commonwealth University developed a fully biodegradable and flexible silk protein fibroin electrode (Pal et al., 2016) that was amenable to photolithographic deposition of conductive polymers including poly(3,4-ethylenedioxythiophene): poly(styrene sulfonate) (PEDOT:PSS). Similarly, silk fibroin materials have been used directly as biodegradable electrodes (Burris et al., 2016), although issues with mechanical durability limit applications. Various labs have developed bottom-up processes for fabrication of electrodes based on materials such as platinum nanowires (Li et al., 2017; D. Zhang et al., 2015) and carbon nanotubes (Claussen et al., 2009). Although these electrodes are not degradable, there is a growing interest in reusing materials for biosensing applications (Abdelbasir et al., 2020), which in the future may include post-processing and recovery of materials from used electronics, including biosensors (Capeness and Horsfall, 2020; European Commission, 2019). This is a concept which is emerging but has not yet been proven at scale.

Enzyme biosensor stability for application in electrochemical devices has been often overlooked or inadequately reported despite being critical to the quality of service and their practical implementation to the FEAST domain for long-term, continuous monitoring of environmental samples, food processing, and along the food supply chain. Three key review papers from US based laboratories reported the stabilization of laccase in ionic liquids (H. Liu et al., 2018), enzyme immobilization on nanoporous gold (Stine, 2017) as well as other strategies that highlight the importance of enzyme stability on the development of commercial biosensors (Reyes-De-Corcuera et al., 2018). The Reyes-De-Corcuera group at University of Georgia combined stabilization effect of high hydrostatic pressure and immobilization of glucose oxidase for an amperometric biosensor resulted in one to two orders of magnitude stabilization (Yang et al., 2020). The Ha group at Washington State University reported the stabilization of pyranose oxidase by a combination of enzyme tethering, enzyme precipitation, and crosslinking with glutaraldehyde (Kim et al. (2017)).

Electrochemical biosensors have advanced considerably in the last 5–10 years, with most efforts in the FEAST domain focusing on pathogens in food or environmental samples (e.g., *E. coli*, *Listeria monocytogenes*, *Salmonella*, *Staphylococcus aureus*, and *Bacillus subtilis*), viruses (hepatitis B virus, influenza virus, zika virus, citrus tristeza virus), agrochemicals (pesticides, nitrogen, potassium) tested in soils, irrigation water, drinking water, and lake/river water. Many recent efforts have focused on development of new sensor platforms (focusing on architecture, arrangement, configuration, DET) and development of low-cost, disposable electrodes for field analysis. Persistent challenges specific to electrochemical sensing include relatively low signal-to-noise ratio in complex matrices, as well as the lack of a unifying approach for discrimination of non-specific binding to the electrode surface. In some modalities (e.g., amperometry, impedance spectroscopy), the requirement for external power is a challenge for in field sensing, for example

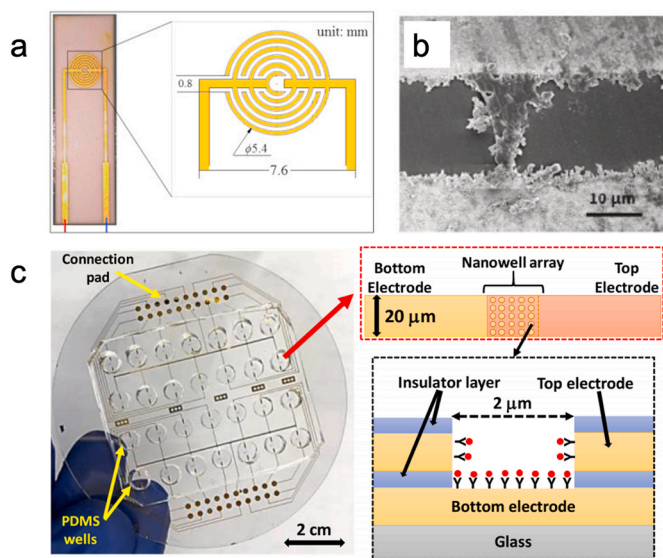


Fig. 7. Innovative electrode arrangements have led to improvements in electrochemical sensing. **a)** Asymmetric electrode arrangements for IDEs; courtesy of Xu et al. (2016), with permission from © Elsevier. **b)** Interlocking nano-wire IDEs; courtesy of Feng et al. (2020), with permission © from Science Direct. **c)** 3D co-planar electrode configurations; courtesy of Mahmoodi et al. (2020), with permission from © IEEE.

the development of continuous “bury-and-measure” soil sensors. Another factor which is challenging in electrochemical sensing is biofouling, which causes noise that must be characterized with non-linear time series analysis (McLamore et al., 2020). Finally, the stability of the biological sensing element, in particular enzymes, remains one of the greatest challenges for continuous monitoring of most analytes relevant to food and agriculture (Reyes-De-Corcuera et al., 2018). Thus, enzyme-free or non-enzymatic electrochemical biosensing with the use of nanomaterials that has intrinsic enzyme-like properties is an emerging topic, as discussed in detail in the review by Wongkaew et al. (2019).

In the next section, we summarize recent advancements in recognition-transduction schemes based on magnetic techniques.

6. Magnetic recognition-transduction schemes

Magnetic transduction has been used for decades in biosensing, but has become increasingly popular in the last five years (Chan and Gu, 2013; Wu et al., 2019, 2020). The most common approach for biosensing is particle/target separation by attaching biorecognition elements to superparamagnetic particles (e.g., SPIONS) that can be aggregated using an external magnetic field, followed by optical/electrochemical transduction (see reviews by (Llandro et al., 2010) and Giouroudi and Kokkinis, 2017). The focus of this review is emerging biosensors that utilize magneto-transduction directly. In this section, we summarize emerging biosensor discoveries based on two key areas: i) rapid nuclear magnetic resonance biosensors, and ii) biosensors based on spin-vortex mechanics; each of which is amenable to portable biosensor development.

6.1. Nuclear magnetic resonance (NMR) biosensors

NMR spectroscopy is a widely used technique for investigating the structures and dynamics of molecules and for magnetic resonance imaging (MRI) (Günther, 2013). While most NMR applications are in medicine, chemistry, and biology, the NMR technique has been used for decades in agricultural and environmental applications as well. Applications in FEAST include studies of plant cell walls, photosynthetic chloroplast membranes, forages, wood cellulose, and soils (Pfeffer and Gerasimowicz, 1989), for example.

The Pines group at the University of Berkeley, the Ralph group at University of Wisconsin-Madison, and the Ramamoorthy group at the University of Michigan are pioneers in NMR and have been pivotal to much of the groundbreaking work. The Pines Group has been a leader in fundamental nanoscale physics and chemistry related to NMR and its use in nanoparticle systems. Examples of recent developments from the Pines group include innovations that span development of a nanoscale ruler (Choi et al., 2017) to ^{129}Xe NMR relaxation sensing mechanisms based on cryptophane cages (Luo and Alcocilja, 2017; Han et al., 2005; Sánchez-López et al., 2020; Gomes et al., 2016). As another guiding light, the Ralph group has applied NMR for characterizing lignin biosynthesis, including identification of new lignin oligomer units (Yue et al., 2016). While this has not yet been applied to biosensing, there is rich knowledge that may be used to study plant cell walls, algae, and many other systems relevant to FEAST. The Manta group at Harvard University, working with an international team of collaborators, developed an NMR-based biosensor for measuring stereospecific methionine (Met) reductase activity. Although this work was in humans, Met and methionine sulfoxide (MetO) play important roles in plants, including: signaling during abiotic and biotic stress, control of ageing, and transmission of ROS-related signaling (Luo and Alcocilja, 2017; Han et al., 2005; Sánchez-López et al., 2020), and extension of the work by the Manta group could lead to new diagnostics for plant health. Though not yet applied in biosensing, the Gradinaru group at the University of Toronto conducted a comparative study to show that both NMR and single-molecule Förster Resonance Energy Transfer (smFRET) provide similar results for characterization of the conformational ensembles of

proteins as a link between their sequences and functions. This important finding paves the way for new innovations in multiplexing, multi-transduction biosensors (Gomes et al., 2020).

Given the scarce use of NMR as a transduction mechanism in biosensing within the FEAST domain, we provide a brief summary of one established working mechanism below (and cite references for further reading as appropriate). The working principle for NMR is rooted in a (nuclear) chemical shift that occurs in molecules as a result of nuclear shielding in the presence of an applied magnetic field; the magnitude is proportional to the strength of the applied external magnetic field (Saitô et al., 2010). Fig. 8a shows an example of how this principle can be used to detect, for example, bacteria in a biosensor format. In the schematic, ^1H atoms (from water molecules) are shown in nuclear spin under an applied magnetic field. Chemical shift tensors facilitate extraction of data representative of the effective magnetic field. In Fig. 8b, the mechanism is repeated in the presence of target bacteria tagged with magnetic particles (e.g., antibody-labeled SPIONS). Antibody-functionalized magnetic nanoparticles (red circles) influence the nucleus spin of ^1H atoms in surrounding water molecules, and thus alter the effective magnetic field. Since the NMR signal is able to penetrate turbid raw samples, sample preparation is simpler and time-saving compared to other techniques (Luo and Alcocilja, 2017).

Examples of NMR applied to biosensing include the Lightner lab at the University of Arizona, where lab-based NMR was used to detect *Vibrio parahaemolyticus* in artificially contaminated shrimp tissues (Hash et al., 2019). A molecular mirroring technique was used in vivo for detecting *V. parahaemolyticus* levels as low as (105 CFU mL⁻¹) within 5 s, establishing the platform as a highly useful tool for high throughput screening of shrimp. In another example, NMR has been used for microbial metabolomics by the Powers group at University of Nebraska-Lincoln (Halouska et al., 2013; Zhang and Powers, 2012). In these studies, NMR was used to trace metabolic pathways and fluxes via exogenous isotope labels, providing multi-target analysis in near real time using a non-invasive approach. Though not traditional biosensing, this example illustrates the use of NMR for detection of organic molecules in complex samples. What traditional NMR lacks in terms of sensitivity (and thus LOD) is made up by the unmatched selectivity. Quantitative data from NMR are highly

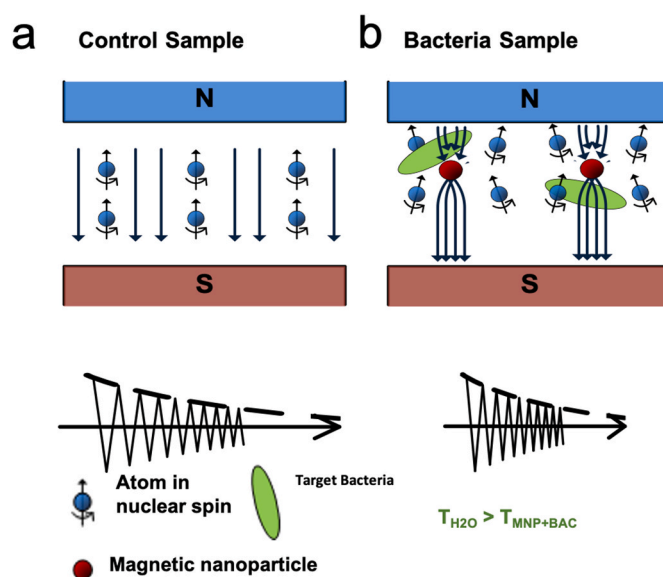


Fig. 8. Schematic showing operating principle of NMR biosensors for detecting bacteria; courtesy of Luo and Alcocilja (2017), reprinted with permission from BMC Springer Nature. a) ^1H atoms of water in nuclear spin. b) illustration of antibody-functionalized magnetic nanoparticles (red circles) adsorbed to bacteria (green rods), in turn influencing the nucleus spin of ^1H atoms in surrounding water molecules. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

reproducible and the operating range is superior to most standard techniques, particularly when studying unknown structures (Markley et al., 2017).

6.2. Superparamagnetic discs for bacteria biosensing

In the last five years, use of superparamagnetic discs has emerged as a sensing mechanism for determination of fluid viscosity (Garraud and Arnold, 2015) or bacteria concentration (Castillo-Torres et al., 2019). The Arnold group at the University of Florida demonstrated selective capture of *E. coli* in various samples using different biorecognition elements (aptamers, lectins) immobilized on disc-sized superparamagnetic discs (Fig. 9). For transduction, numerous fluorescent tags including SYTO9/PI permeability staining, graphene carbon dots were compared to GFP modification. The biosensor was extended by combining with microfluidics for particle sorting and processing of relatively large samples (100 mL), with applications in analysis of drinking water samples or recreational water (Castillo-Torres et al., 2020). The group also showed recovery of the discs with up to 90% efficiency, which is an important feature for scalability. This emerging platform provides an excellent opportunity to use bacteria-sized spin vortex discs as a direct transduction mechanism in a manner similar to Kopelman's work at the University of Michigan (Anker and Kopelman, 2003; Roberts et al., 2005) on SPIONS for cytosolic investigations of mammalian cells. The most compelling aspect of this approach may be the ability to recover the discs and functionalize with different biorecognition agents for simultaneous targeting of more than one cell-surface target.

Hybrid techniques that couple magnetic or chemiluminescent transduction with electrochemical techniques is an area of interest that

has been growing in the last five years (Choi et al., 2016; W. Zhao et al., 2020). For example, the Lee group at Harvard University developed a multichannel chemiluminescent lateral flow assays (LFA) based on magnetic beads for food allergen detection (Lin et al., 2017). While applications of magneto-chemiluminescent biosensors in the FEAST domain are limited (Shahvar et al., 2018a), features such as multiplexing (Li et al., 2020) and portability (Quimbar et al., 2016) are critical for field analysis of food, environmental and agricultural samples.

Biosensors based on magnetic transduction are primarily based on NMR. In the FEAST domain, the applications are limited but new research is paving the way forward for the next decade. NMR biosensors have been developed for bacterial/viral pathogens (malaria, *E. coli*, (Luo and Alocilja, 2017), *Vibrio parahaemolyticus*, *Salmonella*) in food and environmental samples. The most exciting feature of this approach is the ability to penetrate turbid samples, potentially resolving the issue of sample preparation that plagues the field of FEAST biosensors. Use of NMR could open up new analyses with samples ranging from plant/animal tissues, forage/wood cellulose, and soils, milk, and wastewater. Challenges are significant, and primarily in the area of portable NMR platform development as well as sensing protocols for field analysis.

In the next section, we describe recent advancements in mobile (portable) biosensing and also provide examples of innovations in the area of sensing + decision support.

7. Mobile biosensing and analytical systems with embedded decision support

Point of need sensors are a critical tool for monitoring, surveillance, and decision support within the FEAST domain (Datta, 2020c; McLamore et al., 2019; Morgan et al., 2020; Rong et al., 2018; Sidhu et al., 2020). To be practical, point of need biosensors must utilize low cost, widely available technologies for data collection and analysis. In the last decade there have been major efforts by academic research labs and start-up companies to produce viable biosensor products that bring decision support directly to users/stakeholders facilitated by the use of portable biosensor systems (Huang et al., 2018; Roda et al., 2016; Sun and Hall, 2019; Yoon, 2020). Medical and veterinary applications of mobile biosensing are more mature than devices for food, agricultural or environmental sensing (Huang et al., 2018; Neethirajan, 2019), but tools for food safety (particularly for pathogen monitoring) and environmental contaminants are emerging. Beyond portable signal acquisition (raw data), one of the biggest advantages for smartphone-based biosensing is the ability to curate and process data, store results, and instantly share outcomes for a location-specific outcome (Datta, 2020c; McLamore et al., 2019; Morgan et al., 2020; Rong et al., 2018; Sidhu et al., 2020). Below, we summarize recent progress on optical, electrochemical and magnetic biosensors based on smartphones using a system design view (sensor + analytics, or SNAPS). We also highlight tools which have been developed for biosensing + decision support.

7.1. Portable optical biosensors

Colorimetry, fluorometry, bio-imaging, and surface plasmon resonance (SPR) are the most common techniques used in optical biosensing on smartphones. For example, the Yoon lab at University of Arizona developed a tool where the average light intensity from a region of interest is evaluated from an acquired image, and have demonstrated multiple sensor transduction approaches including absorbance and fluorescence with this tool. A miniaturized device employing microfluidic chips was incorporated for portability and rapid analysis of liquid samples (Chung et al., 2019). Both silicone- and paper-based biosensors have been demonstrated with this smartphone sensor system (Park et al., 2013; Stemple et al., 2012) (Fig. 10). Immunochromatographic LFA have also been developed using this smartphone platform (You et al., 2013) (Fig. 10a). Other similar techniques have been used for detection

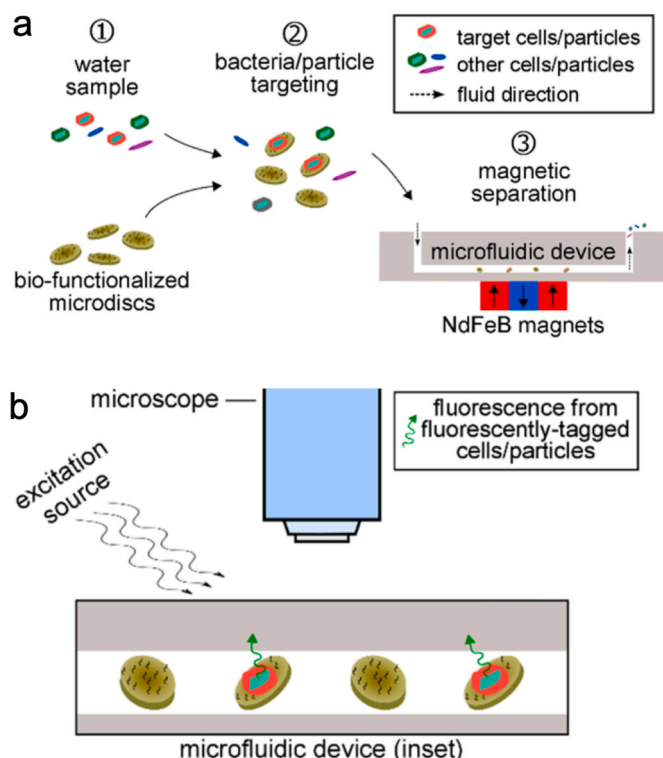


Fig. 9. High-Throughput microfluidic magneto-separation tool for drinking water quality developed by Castillo-Torres et al. (2020). **a)** Water samples are agitated with the aptamer- or lectin-coated superparamagnetic discs to allow for cell/particles binding to discs. The discs are captured within a microfluidic apparatus via a neodymium magnet. **b)** Fluorescence imaging of discs in the microfluidic apparatus. The tool was demonstrated for monitoring drinking water samples of relatively large volumes. Image courtesy of Castillo-Torres et al. (2020) © with permission from MDPI.

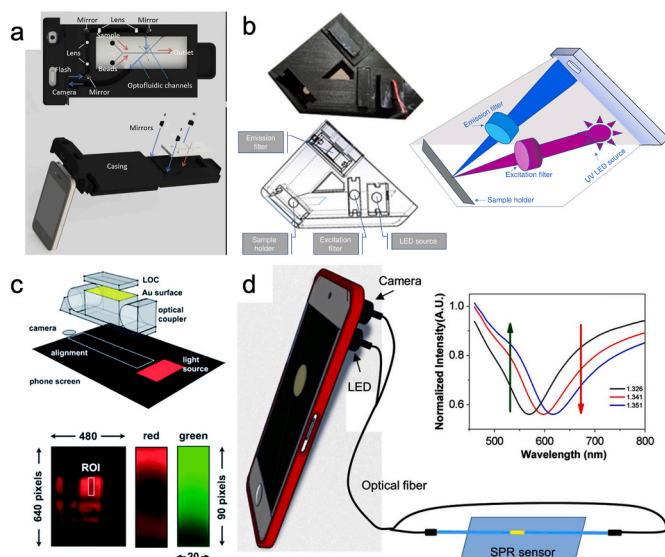


Fig. 10. Optical biosensing using smartphone as a portable platform. **a)** Polydimethylsiloxane-based microfluidic chip encased in a 3D printed enclosure, which guides light from a white LED flash (light source) and collects scattered light from a microfluidic chip for detecting malaria from blood samples. Reprinted from [Stemple et al. \(2012\)](#) with permission from © Sage Publications. **b)** Fluorometer for biosensing based on a customized 3D-printed apparatus with UV LED light source, focusing lens, and excitation/emission filters. Reprinted from [Sarwar et al. \(2019\)](#) with permission from © Nature Publishing Group. **c)** Angle-resolved SPR using a disposable device assembly attached to smartphone and a representative image of red and green ROI. Courtesy of [Preechaburana et al. \(2012\)](#) © Wiley-VCH Verlag GmbH & Co. **d)** Dual color SPR system by [Liu et al. \(2018\)](#) which was used for protein biosensing. Reprinted from [Liu et al. \(2018\)](#) with permission from © SPIE Digital Library. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of *Salmonella* spp. ([Park et al., 2013](#)), and hormones ([You et al., 2013](#)) by the Yoon lab.

Within the FEAST domain, one of the most challenging targets to detect in the field is phosphate ions ([Hashimoto et al., 2014](#); [Negassa et al., 2010](#)). In a biosensing approach, a smartphone fluorometer was developed by the Li group at Florida International University which leverages an environmentally sensitive fluorophore (MDCC) bound to a bacterial phosphate-binding protein to generate a fluorescent signal proportional to the concentration of orthophosphate ([Fig. 10b](#)) ([Sarwar et al., 2019](#)). The focusing lens was designed to match the spot size equivalent to the field-of-view visible through the smartphone camera when aligned in the apparatus. Other recent examples of environmental sensors on smartphones include polybrominated diphenyl ethers developed by the Pan group at University of California Davis ([Chen et al., 2014](#)), among other emerging tools.

In addition to colorimetric and fluorescent sensing, smartphones have been adapted for bio-imaging. Current smartphones are capable of 2x to 4x optical zooms and often include dual, triple, or even quadruple cameras. These features provide significant enhancement in image resolution, on par with mechanical zoomscopes. The Yoon group used this approach to detect norovirus based on counts of the number of immune-agglutinated fluorescent submicron particles from a paper-based microfluidic chip ([Chung et al. \(2019\)](#)). Other recent examples include biosensors developed by the Li group at the University of Arkansas for detection of *Salmonella* ([Wang et al., 2019](#)), and *E. coli* ([Zheng et al., 2019](#)).

A variety of different smartphone-based SPR biosensors have also been developed in the last few years, reviewed by [Lertvachirapaiboon et al. \(2018\)](#) and [Liu et al. \(2015\)](#). Since the first development of an optical fiber assembly by [Preechaburana et al. \(2012\)](#) in Sweden, many

different approaches have been demonstrated (see [Scarano et al., 2010](#) for early pioneering work). [Fig. 10c](#) shows an example of an angle-resolved SPR system with a reported resolution of 2.1×10^{-6} RIU (comparable to commercial compact SPR devices, [Preechaburana et al., 2012](#)). [Fig. 10d](#) shows an example of a low-cost dual color SPR system developed by the Chen lab at Michigan State University ([Liu et al. \(2018\)](#)) which was used for rapid protein biosensing for detection of *Staphylococcus* extracellular protein. Relevant to food, environment and agriculture, SPR biosensors have been developed for analytes ranging from antibodies, to bacterial lipopolysaccharides and pesticides such as imidacloprid, (see review by [Lertvachirapaiboon et al., 2018](#)). The Li lab at Washington State University extended this concept by developing rapid multiplex capabilities for smartphone-based LFA to detect plant viruses ([Wang et al., 2016](#)).

In the next section, we briefly highlight recent efforts in portable biosensors which utilize electrochemical transduction.

7.2. Portable electrochemical biosensors

Development of electrochemical biosensors on a smartphone platform is limited by hardware such as operational amplifiers and other key circuit elements that are not included in smartphones. However, a number of relatively simple external circuits have been developed, allowing signal acquisition through a digital USB connector (wired) or Bluetooth connection (wireless), for example. Most of these external circuits are based on original innovations from the Plaxco group at the University of California Santa Barbara, a tool deemed CheapStat ([Rowe et al., 2011](#)). This potentiostat and other later tools such as DStat ([Dryden and Wheeler, 2015](#)) are limited in terms of number of analytical tests and dependence on physical wire connections. The Baeumner group at Cornell University developed microcontroller-based single measurement devices for analysis such as amperometry ([Kwakye and Baeumner \(2007\)](#)), which has been replicated by a number of groups in the last year for single target applications ([Guan et al., 2019](#); [Mercer et al., 2019](#)). In the last 2 years, the Whitesides group at Harvard University ([Ainla et al., 2018](#); [Jenkins et al., 2019](#)) and the Jenkins group at the University of Hawai'i at Mānoa ([Ainla et al., 2018](#); [Jenkins et al., 2019](#)) developed portable potentiostats that support additional analytical testing capacity. The device by Jenkins et al. can perform CV, EIS, amperometry and voltammetry which is the most comprehensive to date. Also, these new systems communicate with a local smartphone via Bluetooth, which provides considerable advantages over WiFi communication for ensuring data security and cyber security.

The Gomes (Iowa State University) and McLamore (Clemson University) labs developed a smartphone-based biochip system for in-pipe detection of *Listeria* spp. in hydroponic lettuce water ([Sidhu et al., 2020](#)). A platinum interdigitated microelectrode (Pt-IME) biochip was incorporated into a particle/sediment trap for the real-time analysis of flowing irrigation water in a hydroponic lettuce system and data were acquired via Bluetooth using the ABE-STAT system developed by the Jenkins lab (Hawai'i at Mānoa). The aptasensors had a LOD of approximately 50 CFU mL⁻¹ with a linear range up to 10⁴ CFU mL⁻¹. The group also collaborated to expand this tool by developing a partially autonomous SNAPS system for hydroponic water analysis targeting *E. coli*. Biosensors were developed using lectins and antibodies on reduced-graphene-Pt electrodes, and the ABE-STAT system was used for data acquisition on a smartphone. The LOD was 50 CFU mL⁻¹ and the response time (including pumping and actuation) was 20 min in hydroponic water for fresh produce ([Giacobassi et al., 2021](#)). This proof-of-concept system extends the SNAPS paradigm by providing autonomy and is known as the Sense-Analyze-Respond-Actuate (SARA) system. uses a biomimetic nanostructure that is analyzed and actuated with a smartphone.

The Hart lab from the Massachusetts Institute of Technology developed a low-cost portable biosensor system for soil analysis based on solid state ion-selective electrodes (ssISE) containing valinomycin as a

biorecognition material. The sensors were near-Nernstian with a LOD of 24 ppb (Rosenberg et al., 2018) and correlated to standard analytical techniques for soil samples taken at the local campus. In another example, the Neethirajan lab at the University of Guelph developed a portable biosensor based on screen printed electrode for rapid diagnostics of animal health in the field (Tuteja et al., 2018), and the low-cost device was comparable to an ELISA test.

In the next section, we briefly highlight recent efforts in portable biosensors which utilize magnetic transduction.

7.3. Portable NMR biosensors

Early NMR biosensors were lab-based, using bulky and expensive instruments (Ng, 2015). More recent instrument developments have focused on portability such as the work by Luo and Alocilja at Michigan State University (Luo and Alocilja, 2017; Yu et al., 2009). Development of portable NMR (pNMR) and high-throughput NMR spectrometers facilitate analysis of silicon chips which are 2 mm by 2 mm (Ha et al., 2014; Patel, 2014). Early work with pNMR in medical applications was based on NMR relaxation time (Lee et al., 2008), which has been extended to show noninvasive spin-echo imaging of living plants in their natural environment (Rokitta et al., 2000), for detecting disease biomarkers (Lee et al., 2009; N. Sun et al., 2009), malaria parasites (Peng et al., 2014), and immune-markers linked to pathogen infection (Sullivan and Prorok, 2015), in addition to other examples (Haun et al., 2011). A few recent pNMRs have been integrated with microfluidic sorting such as the micro NMR (μ NMR) relaxometer, which integrates microfluidics inside a portable sub-Tesla magnet (K.-M. Lei et al., 2015).

Luo and Alocilja at Michigan State University developed a pNMR for detecting foodborne bacteria in water and food matrix, particularly *E. coli* O157:H7 (Luo and Alocilja, 2017). The principle is illustrated in Fig. 11, where antibody-functionalized magnetic nanoparticles shift the nearby field strength and magnetic field uniformity and affect the nucleus spin of hydrogen (^1H) atoms in surrounding water molecules, leading to a decrease in precession decay rate of the nuclear spin. In this design, the NMR biosensor measures the spin-spin relaxation time of water protons in proximity to the magnetic nanoparticles in the test sample. The LOD for milk and water was in the order of 10^1 CFU mL^{-1} and the range was 10^1 CFU mL^{-1} to 10^7 CFU mL^{-1} .

While the sensor engineering advancements discussed above are critical, sensor data without decision support is of limited value to users (see reviews for details McLamore et al., 2019; Morgan et al., 2020). Progress in cyber-physical systems (e.g., SNAPS, SARA) must be balanced by an equivalent focus on real-time edge/fog analytics for providing quality of service to users. In the next section, we briefly highlight recent efforts to embed data analytics and decision support using smartphone applications.

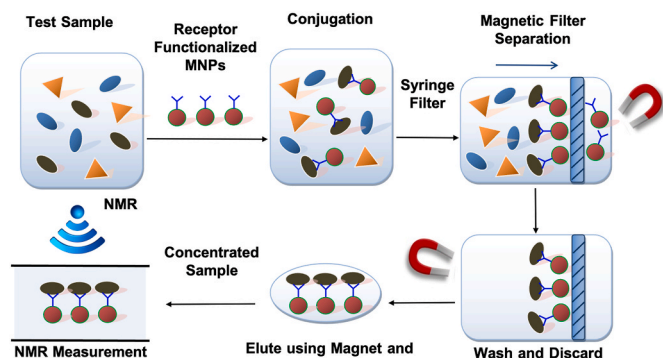


Fig. 11. Schematic of the portable NMR biosensor by Luo and Alocilja (2017) and sample preparation with detection using the pNMR biosensor; reprinted with permission from BMC Springer Nature.

7.4. Smartphone biosensors with embedded decision support

To maintain the integrity of user needs and ensure quality of service, modern tools should embed key aspects of decision support tools (Sutton et al., 2020). In FEAST applications, this is critically important as the point of analysis is often hours, sometimes days, away from an analytical laboratory or field station. While smartphones cannot provide high performance computing on site, simple calculations can be made for development of artificial reasoning tools (ART) or other “traffic light” decision support systems connected to biosensor data. A variety of open-source packages are available in universal languages such as R and Python. Further, open-source platforms such as Thunkable and MIT app inventor utilize block (Scratch) coding, which does not require extensive training for app developers.

For example, the McLamore group at Clemson University develop a series of simple applications in Thunkable using the ABE-Stat developed by the Jenkins lab (see previous section for description of biosensor chemistries). Applications developed to date include analysis of heavy metals in drinking water, which also contains feedback to the user regarding basic risk analysis (McLamore et al., 2019) (Fig. 12a). Other examples include applications for calculating concentration of *Listeria spp.* (Sidhu et al., 2020) and *E. coli* (Datta, 2020c) on fresh produce by analyzing aptasensor data and comparing outcome(s) to the produce safety rule set by the U.S. Food and Drug Administration Fig. 12b). While these simple tools are useful for connecting users to the outcome of the biosensor data, the meaningful use is limited in that statistical analysis is lacking. To resolve this, Rong et al. (2018) developed an app for



Fig. 12. Examples of SNAPS for on-site sensing with embedded data analytics and decision support. a) Electrochemical aptasensor for detection of heavy metals in drinking water; reprinted from McLamore et al. (2019) with permission from © MDPI. b) Impedimetric aptasensor for measuring *Listeria spp.* in fresh produce samples; reprinted from McLamore et al. (2019) with permission from © MDPI. c) Smartphone machine learning analytics for sample classification in small protein sensing; reprinted from Rong et al. (2018) with permission from © Royal Society of Chemistry. d) Impedimetric biosensor for measuring SARS-CoV-2 on surfaces using the human receptor ACE-2; reprinted from Datta et al. (2020) with permission from © MIT Libraries.

embedding machine learning (support vector classification) into the applications (Fig. 12c); the step-by-step procedures for coding the tool in Python were provided in multiple languages, including English, Spanish, Portuguese, and Chinese. A first-generation app was also developed for decision support linked to detection of SARS-CoV-2 (Fig. 12d) (Datta, 2020b).

Whether electrochemical, optical, or magnetic transduction is used in biosensor development, use of new/unique materials comes with the added risk of causing environmental or ecological damage (particularly if the sensor is disposed on site or used for long term in-field monitoring). Thus, no discussion of biosensor research progress is complete without a discussion of material safety (sensor fabrication) and material fate and transport. In the next section, we review recent developments in the area of materials safety as it relates to biosensor design, including challenges associated with scale up.

8. Life cycle, and environmental and health safety

The performance of biosensors is known to be enhanced when nanomaterials are incorporated in at least one active component (e.g., electroactive materials, photocatalysts, superparamagnetic materials) (Holzinger et al., 2014; Soleymani and Li, 2017). However, some unique materials may pose a risk of negative environmental (Clar et al., 2016; Pini et al., 2017; Wigger et al., 2015; Palmqvist et al., 2015; Reed et al., 2016; Zamengo et al., 2020; Gottschalk and Nowack, 2011; Bolyard et al., 2013; Part et al., 2020; Polesel et al., 2018; Benn et al., 2010; Meier et al., 2016; Gómez-Rivera et al., 2012) and/or mammalian (Bartucci et al., 2020; Kolosnjaj-Tabi et al., 2015; Kuempel et al., 2012; Kuka et al., 2016; Pini et al., 2017; Rasel et al., 2019; Sayes et al., 2017; Shannahan and Brown, 2014; Zamengo et al., 2020) impacts. As new biosensors are developed for the food industry (namely packaging), these risk pathways expand considerably. To date, there have been limited regulations, industry standards, and industry guidelines governing the production of nanomaterials. In this section, we briefly summarize the relevant regulations, recent progress in understanding life cycle and fate of nanomaterials in the environment, and we also discuss database(s) that can be consulted when choosing materials for biosensor development and supporting hardware such as batteries and circuitry.

8.1. Current regulations for nanomaterials

In 2017, the EPA issued a final rule under the Toxic Substances Control Act which requires companies that manufacture, intend to manufacture, process, or intend to process certain nanoscale chemical substances report and maintain records for 3 years regarding the specific chemical identity, production volume, method of manufacture and processing, exposure and release, and information concerning the environmental and health effects (40 CFR 704; US EPA, 2017). The Nanotechnologies Technical Committee (TC 229) is under the International Organization for Standardization (ISO). ISO/TC 229 Working Group 3 is responsible for developing the industry standards for Health, Safety and Environmental Aspects of Nanotechnologies. The Committee has published several technical reports, e.g., ISO/TR 11360:2010 (Methodology for the classification and categorization of nanomaterials), 13121:2011 (Nanomaterial risk evaluation), 13014:2012 (Guidance on physico-chemical characterization of engineered nanoscale materials for toxicologic assessment), 12885:2018 (Health and safety practices in occupational settings), etc. The International Electrotechnical Commission also has the Technical Committee (TC 113) that focus on the development of standards for Nanotechnology for Electrotechnical Products and Systems. In addition, the American Society for Testing and Materials has Committee E56 on Nanotechnology whose mission is to address issues related to standards and guidance materials for nanotechnology and nanomaterials.

8.2. Life cycle and environmental fate

Life cycle assessment (LCA) is foundational for considering the potential environmental impact and health safety of materials used in fabrication of a biosensor (Donia and Carbone, 2019; Stensberg et al., 2011). LCA considers the life-span of materials utilized for manufacturing, utilization, waste materials generated during manufacturing (Som et al., 2010), re-use, recycling, recovery, and final disposal (Lazarevic and Finnveden, 2013). During the manufacturing process, relevant exposure pathways include inhalation (Guo et al., 2018; Iavicoli et al., 2020; Jakobsson et al., 2018; Kendall and Holgate, 2012; Poh et al., 2018; Schwotzer et al., 2018; Sturm, 2015; Svensson et al., 2013), accidental ingestion (Guo et al., 2017; Richter et al., 2018; Smock et al., 2014), and dermal contact (Auttachoat et al., 2014; Gepfert et al., 2020; Hadrup et al., 2018; Ryu et al., 2014; Shepard and Brenner, 2014; Singh et al., 2017). Numerous reviews summarized possible adverse human health effects related to workplace safety specific to nanomaterials (Ferdous and Nemmar, 2020; Iavicoli et al., 2020; Smolkova et al., 2015; Teow et al., 2011; Xia et al., 2009). In general, exposure pathways for biosensor users are limited to point-of-care applications or implanted biosensors (Gray et al., 2019; Scholten and Meng, 2018; Y. Sun et al., 2009; Wisniewski et al., 2000), as laboratory detection and clinical/field diagnostics pose minimal risks for exposure. The salient environmental and human health risk is associated with nanomaterial waste generated during production and disposal stages. Waste discharged into sewer pipes or deposited in landfills poses a threat of leaching. However, perhaps a more concerning pathway is the common use of incineration for sewage sludge management, causing phase transfer to particulate and/or aerosol that can be dispersed by wind. The potential for air pollution due to aerosols generated during wastewater treatment and incineration may pose a major risk.

In addition to the aerosol route, there is a direct connection to agriculture as 60% of the total sludge in the USA is applied to agricultural soils as an amendment (US EPA, 1995). Once applied to soil, nanoparticles associated with disposed biosolids are ultimately bioavailable for uptake by microbes, plants, and animals; potential for additional transfer among trophic levels in food webs can also occur via bioaccumulation and biomagnification (Laban et al., 2010; Stensberg et al., 2014a, 2014b). Thus, the main potential environmental impacts associated with biosensors likely originate from materials discharged to wastewater. Nanophase Au, Ag, Cu, TiO₂, and CeO₂ have been shown to enter wastewater treatment plants (WWTP), each of these is commonly used in biosensor development. Many studies show that these materials are removed along with biosolids (i.e., sludge) (Ganesh et al., 2010; Kaegi et al., 2011; Wang et al., 2012; Gómez-Rivera et al., 2012; McLamore et al., 2020), which is incinerated and ultimately dispersed with aerosols/particulate matter or deposited onto agricultural soils. AgNPs represent the largest risk to the environment due to their toxicity at environmentally relevant concentrations and the largest number of consumer products with Ag containing nanomaterials compared to other nanomaterials (Vance et al., 2015). The environmental concentration for Ag in freshwater are predicted to increase up to six-fold by 2050 (Giese et al., 2018). Nanomaterials undergo transformations when they enter in contact with wastewater and soils, because both environments are enriched with sulphur and phosphorous, which as a result affect their bioavailability and toxicity (Lv et al., 2012; Ma et al., 2014).

Multiple studies demonstrated that nanomaterials, including Au, Ag, ZnO and CuO can be taken up by plants and transferred from roots to distal part of the plant via apoplastic (intracellular space) or symplastic (cell-to-cell) pathways (Geisler-Lee et al., 2012; Zhai et al., 2014). A recent study with stable AuNPs showed that microbiome of aquatic plants can facilitate dissolution of AuNPs in aquatic wetland systems (Avellan et al., 2018). Bioaccumulation of AuNPs was observed from aquatic plants into *Daphnia* (Lee et al., 2015). Another experiment with simulated estuarine mesocosms found bioaccumulation of AuNPs in clams (Ferry et al., 2009).

The first evidence for trophic transfer of AuNPs with biomagnification in a terrestrial system was shown for tomato and tobacco plants to tobacco hornworms *Manduca sexta* (Judy et al., 2011, 2012). Engineered nanomaterials may migrate through and persist in the ecosystems influencing the dynamic interaction between the environment and members of the ecosystems including viruses, bacteria, fungi, plants, insects, and animals (Bieler-Fraser et al., 2014; Adams et al., 2006; Katsumiti et al., 2018; Kumari et al., 2014; Du et al., 2020; Frenk et al., 2013; Manna and Bandyopadhyay, 2017; Xu et al., 2018; Du et al., 2019; You et al., 2011; J. Liu et al., 2018; Kanold et al., 2016; Bundschuh et al., 2019; Alkhatib et al., 2019; Shang et al., 2020; Du et al., 2018; Liu et al., 2019; Asztemborska et al., 2018; Özel et al., 2014). Although not reviewed in detail here, many engineered metal containing nanomaterials have antimicrobial properties, which may contribute to antimicrobial resistance via increase in horizontal gene transfer or development of cross-resistance (Cesare et al., 2016; Zhang et al., 2018). Toxicity to aquatic and terrestrial organisms is also a major concern for nanomaterials used for biosensor development (reviewed in detail elsewhere in Asghari et al., 2012; Collin et al., 2016; Schultz et al., 2016; Tsyusko et al., 2012; Völker et al., 2013).

In the next section, we briefly outline the relevant databases recently developed in North America for environmental health and safety of engineered nanomaterials (focusing only on databases related to biosensor development).

8.3. Environmental risk and safety databases

Numerous databases exist for serving as a repository for information on toxicity of pristine nanomaterials and transformed nanomaterials. For example, NanoInformatics Knowledge Commons (NIKC) was developed by the Center for Environmental Implications of Nanotechnology (CEINT) at Duke University (Karcher et al., 2018). The Nanoinfo database was developed by the Center for Environmental Implications of Nanotechnology (CEIN) at the University of California Los Angeles. Information on health and safety specific to manufacturers and users can be found in the Nanoparticle Information Library (NIL) (<http://nanoparticlelibrary.net/nil.html>), developed and run under National Institute for Occupational Safety and Health (NIOSH). A repository known as caNanoLab (<https://cananolab.nci.nih.gov/caNanoLab/>) is supported by the National Cancer Institute, and is the data sharing source specific to the use of nanomaterials in medicine. Additional health risk information is available within the ISA-TAB-Nano database. When selecting nanomaterials for use in biosensors, it is imperative to take into consideration their environmental risk and human health effects and select the safer option. This can be achieved by reviewing available databases and published studies, as well as existing regulations pertinent to these nanomaterials. These databases need to be integrated in the design of biosensors for FEAST.

In the next section, we summarize the challenges and future perspectives on the horizon for FEAST biosensors.

9. Challenges and future perspectives

Over 100 manuscripts describing biosensors developed by labs in North America were reviewed. While this is by no means a comprehensive study, the trends derived from the analysis support reviews by Griesche and Baeumner (2020) and Justino et al. (2017). Innovations in biosensor research related to food systems (i.e., post-harvest), environmental and agricultural production are quite limited in terms of the number of targets. Most groups in North America focused on pathogen detection in food. Optical and electrochemical biosensors were the dominant form of transduction, but magnetic devices are emerging. Most of the manuscripts reviewed here (approximately 40%) focused on fundamental technology development, with biosensor research in the areas of food and environmental applications each comprising approximately 25% of the manuscripts. Biosensors applied to agricultural

production represented only 15% of the reported manuscripts in the last five years. For additional details, see Table S1 in supplemental section.

Emerging opportunities and challenges for biosensing research (Table 1) are organized by food (F), environment (E), agriculture (A), and sensing technology core developments (ST) as they relate to the PEAS platform. Prior to consideration of common biosensor design issues (e.g., bioreceptor selection, biocompatibility of materials, sample matrix issues, etc.), sensor design teams must devote considerable effort to determining what users (e.g., food consumers, citizens using public services, workers, regulatory agencies) desire in terms of device performance. Key performance indicators must be established *a priori* so that biosensor performance may shift focus toward quality of service (QoS) that is attributable to biosensor data.

9.1. Food system biosensors (post-harvest)

Over half of the biosensors analyzed in this review for applications in post-harvest food systems utilized optical transduction approaches, and most were either SERS or LSPR (film based). Among the biosensors reviewed, use of NMR and superparamagnetic discs are innovative transduction mechanisms for applications in food samples. A majority of the biosensors were designed for detection of bacteria pathogens, which is the same conclusion drawn by Griesche and Baeumner (2020), and we also note a lack of diversity in the important targets reported over the last decade. A number of smartphone-based biosensors have been developed outside of North America for targeting bacteria (Wang et al., 2019), chemical toxins (X. Li et al., 2019), allergens (Ludwig et al., 2015; Ross et al., 2018), and adulterants (Shahvar et al., 2018b).

Matrix issues continue to be the most salient challenge for biosensors in post-harvest applications. For pathogens, many reports in the last decade do not test reliability based on federal guidelines (Canada Food Inspection Agency, 2020, US FDA, 2018, US FDA, 2020). Beyond bacteria detection, there are guidelines for other regulated targets and these must be strictly adhered to. These guidelines are within the Food Safety Modernization Act (US Congress, 2011), the regulations enacted under the Safe Food for Canadians Act (Canadian Parliament, 2012) and the two regulatory bodies in Mexico: the Federal Commission for the Protection from Sanitary Risks (COFEPRIS) and the National Service of Agro-Alimentary Health, Safety and Quality (SENASICA) (Leon and Paz, 2014). To date, there is no consensus on how to handle nanomaterials from biosensors across these regulatory bodies, but the existing governance was summarized in our review.

As noted by Ross et al. (2018), design of user-friendly optical biosensor devices is critical for commercialization in the food industry. Use of a common smartphone for detection of contaminants within the food chain is complicated by federal regulations that govern reporting standards and food recalls. Platform tools are emerging for connecting users to appropriate technologies (discussed below), but these efforts are not yet mainstream in North America.

9.2. Environmental biosensors

Most of the biosensors with environmental applications analyzed herein were based on optical transduction, and the remainder were primarily magnetic. Nearly half of the devices were portable and targets included waterborne pathogens, heavy metals, environmental biofilms, and toxins such as organo-bromines. Outside of North America, numerous portable biosensors were developed for targets such as ions in river water (Dutta et al., 2015), *E. coli* in drinking water (S. Li et al., 2019), and cyanotoxins in water bodies (Z. Li et al., 2019). McConnell et al. at McMaster University (Canada) (McConnell et al., 2020) provide a comprehensive review of aptasensors used in environmental monitoring (including air and aqueous samples), which is an area of high interest given the stability of aptamers over antibodies (particularly in field studies). McConnell highlight portable devices as a critical need and discuss specific challenges in translating lab scale discoveries to *in situ*

Table 1

Key challenges and opportunities for biosensing in food, environmental, and agricultural domains.

Topic	Domain	Challenges	Opportunities
(F) Food	Matrix issues	- Analysis in large volumes of food, particularly for microfluidics - Lack of non-invasive, non-destructive sampling techniques - Signal hysteresis and device reusability	- New federal food safety guidelines released by US and Canada - New partnerships between US and Mexico for food safety regulation
	Decision support	- Data security/privacy - Federal regulations that govern reporting and food recalls deter some stakeholders - Lack of open-source database	- Smartphone-based artificial reasoning tools (ART) - New paradigms in real-time decision support - Embedding regulatory standards into apps
	Material life cycle and EH&S	- No consensus on how to handle nanomaterials from biosensors - Lack of tools for characterizing fate and transport of nanomaterials across the supply chain	- New informatic tools for connecting diverse databases
(E) Environment	Matrix issues	- Adherence to minimum sampling volume guideline, particularly for microfluidics - Data analysis for grab samples versus continuous sampling - Signal hysteresis and device reusability and longevity	- Incorporation of biosensors within water treatment systems (smart technology)- UAV for data acquisition facilitates high spatiotemporal monitoring
	Decision support	- Data security/privacy - Federal regulations that govern reporting and land ownership are complex - Lack of open-source database	- Smartphone-based artificial reasoning tools (ART) - New paradigms in real time decision support - Participatory monitoring programs (i.e., citizen science) - Connecting water/soil body characteristics acquired by remote sensing with biosensor ground truthing - New informatic tools for connecting diverse databases
	Material life cycle and EH&S	- No consensus on how to handle nanomaterials from biosensors - Lack of tools for characterizing fate and transport of nanomaterials in environment	
(A) Agriculture	Matrix issues	- Biosensors designed for bacteria detection must meet, at a minimum, commodity-specific regulatory requirements such as the produce safety rule for microbial water quality, i. e., at least 100 mL sample volume	- pNMR sensing platforms can be applied for plant tissue and water analysis - multi-tool approaches for resolving issues with soil complexity - UAV for data acquisition facilitates high spatiotemporal monitoring - increase demand by stakeholders for sustainable practices, resulting in increased efforts to monitor environmental parameters (plant, soil, air, and water quality).
	Decision support	- Data security/privacy - Federal regulations that govern reporting and land ownership are complex - Lack of open-source database	- Smartphone-based artificial reasoning tools (ART) - New paradigms in real-time decision support- Connecting plant and soil traits acquired by remote sensing with biosensor ground truthing - New informatic tools for connecting diverse databases
	Material life cycle and EH&S	- No consensus on how to handle nanomaterials from biosensors - Lack of tools for characterizing fate and transport of nanomaterials in production systems	
(ST) Sensing Technology Core Developments	Optical biosensors	- <i>in situ</i> control over dielectric behavior of SERS substrate - standards for sample processing - lack of reference spectra database	- Label-free high throughput screening for numerous analytes - Detection of bacteria as low as 1 CFU mL⁻¹ (SERS) - Diverse targets possible - Amenable to multiplexing - Direct integration with integrated circuit systems for actuation (e.g., SARA) - Label-free detection of bacteria and viruses in food or environmental samples - Low-cost electrodes for field analysis (in some cases compostable) - Amenable to multiplexing
	Electrochemical biosensors	- Relatively low signal-to-noise ratio - Requirement for external power (e.g., amperometry, impedance spectroscopy) - Discrimination of non-specific binding in complex matrices - Bioelectric noise from biofouling	- Label-free NMR biosensors for bacterial/viral pathogens - Ability to penetrate turbid and viscous samples may resolve sample preparation issues
	Magnetic biosensors	- Enhanced pNMR platform development - Proven sensing protocols for field analysis - Reducing cost for pNMR	- Functioning IoT proof-of-principle examples - Open-source tools for analytics and algorithms for data and information arbitrage - Data-informed decision as a service (DIDAS)
	PEAS platform (section 2)	- Dynamic connectivity amongst sensor networks, analytical systems, and decision support systems - Robust example of operational abilities - Interoperability between food, environment and agriculture specific sub-platforms - Convergence of material informatics with sensor engineering - Shift toward use-inspired sensor design	- new health paradigms based on integration of food/environment/agriculture biosensing with established medical platform(s) - Sensors for providing intra- and inter-connectivity amongst nodes of FEWSH

EH&S = Environmental and Health Safety.

FEWSH = food-energy-water-sanitation-health nexus.

UAV = unmanned aerial vehicle.

detection, which is the same conclusion drawn from this review.

Matrix issues and poor sensor selectivity are challenges within the field of environmental monitoring, and this problem may be exacerbated

as many published papers that describe use of drinking water samples do not conform to federal regulatory testing standards (including secondary validation). If drinking water samples are tested, one of the challenging

criteria that must be adhered to is the minimum sampling volume guideline (US EPA, 2015). In field sampling, the issue is even more problematic, particularly for devices that claim to have low hysteresis and are amenable to continuous measurement *in situ*. Sampling strategies must, at a minimum, aim to capture the high variability and spatial heterogeneity of small molecules, viruses and cells in the environment.

Beyond sensor design and matrix issues, other challenges to environmental monitoring that affect biosensor research are related to data. The most important issues related to sensor data include: i) data privacy and security, ii) legal and political issues associated with land ownership and rights, iii) the lack of a publicly accessible, trusted, open-source data repository for sensor data, and iii) lack of guidance for biosensors designed for point-of-care testing versus discrete population testing. Given these challenges, participatory monitoring programs (i.e., citizen science) face many uphill struggles but this approach has been gaining momentum over the last few decades, and more progress is anticipated with the further development of smartphone-based biosensors and the inclusion of decision support systems embedded into the mobile device.

9.3. Agricultural biosensors

In agricultural production, biosensors have not matured to the same level as post-harvest and environmental applications. A majority of the biosensors were electrochemical, and, to date, there were no magnetic biosensors analyzed which have application in agricultural sensing. Portable NMR devices for medical (human) diagnostics in rural setting have been developed, and the relevant conditions are closely associated with animal agriculture (e.g., tuberculosis diagnosis). It is anticipated that these portable magnetic biosensors will pave the way for other targets in agricultural production based on the plethora of laboratory studies on plant systems using NMR and MRI. One of the most attractive features of NMR as a biosensing platform is the non-invasive nature of the analysis, together with the ability to process samples of various rheology and physical attributes. Outside of North America, mobile biosensors were developed for various agricultural targets, including pesticides (Montali et al., 2020), plant-wearable biosensors (F. Zhao et al., 2020), heavy metals in soils (Liu et al., 2020), and multiplexing sensors using data fusion (Marcu et al., 2020).

Biosensors designed for bacteria detection must meet, at a minimum, commodity-specific regulatory requirements such as the produce safety rule for microbial water quality (US FDA, 2015). Processing a sample volume of at least 100 mL is not trivial, particularly when using microfluidics and these practical issues must not be overlooked by sensor developers if progress toward technology translation is the goal.

One of the potential strengths of agricultural biosensing is the strong network of researchers and extension specialists who have been studying technology appropriation (Rutten et al., 2018; Useche et al., 2009, 2013). The possibility of new WiFi systems for rural environments is a major opportunity that looms for “smart farming”, but in some cases this could be resolved by use of UAVs for near field communication. While not true in all cases, there is a general assumption within most studies that growers and stakeholders in agricultural production do not have time to dedicate towards application of sensors within the routine workday. This pushes biosensor design teams to develop applied strategies which are either based on: i) or ii) partial autonomy of data collection and analytics. In either case, next generation smartphone biosensors in agriculture should be coupled with decision support systems and, when possible, statistical analysis of replicate samples.

9.4. Sensing technology core developments

Studies of biosensor platforms (e.g., nanohole arrays, flexible electrodes, mobile sensing devices) represented most of the research analyzed in this review. The architecture and pattern of the active sensing are strong areas of progress over the last decade, and new approaches may improve sensing performance in more than one

application space. Exciting opportunities to integrate biosensors within wireless sensor networks (in some cases facilitated by semi-autonomous robots) using the IoT design metaphor may energize the field in the next decade. In the closing sections below, we present a call for four critical sub-platforms that may facilitate such developments.

9.5. Use-inspired sensor design and the triple bottom line

In addition to mass-distributed concepts, the commercial market for biosensors in food, environment and agriculture is growing quickly, primarily in the area of point-of-care technologies (GVR, 2020). Classic frameworks such as the recognition-transduction-acquisition (RTA) triad will always govern biosensor behavior at the molecular level (McLamore et al., 2019), but design should also be guided by societal drivers (Ross et al., 2018). One popular design framework is the triple bottom line (TBL) concept, focused on economic, environmental and social values. In regards to the economic framework for biosensor development, concepts such as pay-a-penny-per-use (PAPPU) (Morgan et al., 2020) have been established for smartphone sensors. Environmental considerations for use of new materials and disposal of single use sensors are governed by national and local regulations. When selecting nanomaterials for use in biosensors, it is imperative to take into consideration the environmental risk and human health effects associated with the material. The third pillar of the TBL framework, social value, is perhaps the most critical for ensuring meaningful use of biosensor technologies. While databases exist for economic and environmental pillars of the TBL triad, social relevance is not well characterized.

In biosensor research, risk of adverse health and safety effects linked to a material are most likely associated with the manufacture stage (agricultural production, environmental sensing, or food packaging). Many modern biosensor laboratories not only design new recognition-transduction schemes, but also fabricate the sensor device and associated components in-house (made possible by mainstream access to 3D printers, inkjet printers, embossing, metal deposition techniques, etc.). Streamlined end-to-end fabrication and testing are exciting and evoke innovation, and biosensor research laboratories have benefitted greatly in the last five years. This advancement is a cautionary tale, and comes with the added responsibility of ensuring that a specific biosensor design (from inception to prototype development) considers the release of materials to water, air, soil or food systems as well as their toxicity to organisms inhabiting these environments and to human health. Tools for interfacing with databases describing NP behavior, fate and toxicity, may help avoid use of nanomaterials with evidence for toxicity at low concentrations (e.g., AgNPs).

9.6. Interoperability between food, environment and agriculture sub-platforms

Lessons from healthcare warn that interoperability of tools (see interface layer shown in supplemental section Fig S9–S10) must be a design consideration from conception. Interoperability standards may help to ensure that data fusion can be initiated on demand to adapt to the increasing complexity of the environment interrelationships, and balance the outcome with respect to the context of the subject or use case. To ensure interoperability of sensor data from different FEAST domains, the correct biosensor must first be matched with the appropriate stakeholder/user need. One opportunity for addressing this problem is the development of a sensor discovery engine that matches the correct sensor to the specific question by exploring databases of available devices. The skeleton of one such database, the sensor search engine (SENSEE) has recently been developed by the McLamore group at Clemson University (McLamore, 2019a, 2019b). When combined with portfolio analyses such as multicriteria decision analysis (MCDA) (Sidhu et al., 2020), SENSEE may allow users to search for information with respect to appropriate tools and rank the technologies based on user

needs, similar to NASA's mission-specific technology readiness level (TRL) hierarchy. Once the appropriate sensor is matched to the stakeholder/user need, data collected in a synchronous or asynchronous fashion may be interfaced into the PEAS platform.

Interoperability depends on connection of multiple databases, specifically three types of data: i) individual nodes of P-E-A-S, ii) life cycle and environmental health and safety, and iii) local, regional and/or national regulations. Connecting data for sensor percepts (features such as sensitivity, LOD, operating range, response time, hysteresis, cost, perceived usefulness, etc.) with environmental data (biological/physical/chemical operational data for land, sea, air and/or water) is not trivial, but may be the lowest hanging fruit. Dynamic environmental factors alone represent a major challenge in data interoperability and real-time situational analysis and to date there are few successful examples of interfacing micro-weather stations with other real-time data systems. The sensing node may connect biosensor data (structured, unstructured, or hybrid) to a specific problem that has associated environmental/life cycle and regulatory constraints (e.g., restrictions on burying sensors in soil, flight path restrictions for UAVs, etc.). In some cases, an operational system may be designed with these nodes, but will have limited actionable information without the actuation layer. This layer is by far the most complex from a design perspective, and requires multiple cyber security and data security layers.

Translating these ideas to the food-environment-agriculture domains is a pressing need in the next decade. Holmes et al. (2018), among others, called for new innovations in health and supply chain surveillance prior to the onset of the current COVID-19 pandemic, but this was not realized. In a post-pandemic world, this need is even more critical (Datta et al., 2020), and monitoring tools such as biosensors are needed to cross silos within the food-energy-water (FEW) nexus. When combined with analytics, sensors are the key tool for creating new bridges to convergent paradigms of a food-energy-water-sanitation-health (FEWSH) nexus that extends the concept. This type of systems-approach to biosensor development is expected to be a major driving force to address the complexity of real-world problems that require a technology foundation that is both adaptable and resilient.

10. Concluding remarks

Combined sensor/analytics platforms must be developed with common portable instruments such as smartphones. In the next evolutionary step, platforms such as PEAS can serve as a pillar upon which to build bridges forward. PEAS provides excellent guidance based on lessons learned from the medical domain, and demonstrates the importance of dynamic connectivity amongst sensor networks, analytical systems, and decision support systems. In this review, we build upon recent reviews and merge the ideas to create a list of seven key actions in the areas of sensor autonomy, technology translation, and interoperability (see Figure S11). The concepts within the call for action are by no means new, but the necessary components are anticipated to converge in the next 5–10 years for realizing these ideas.

Presently, the FEAST of biosensors has produced a wealth of opportunity but faces a famine of actionable information if convergence with data analytics and decision support are not realized. There is enormous opportunity for new devices that may emerge from these meta-domains, but the path ahead is not trivial and biosensor researchers must diligently focus efforts toward delivery of reliable information as a service to society. The field should focus on diversifying the quantity of targets, enhancing partial autonomy, and contributing to platform development for improving interoperability amongst devices.

CRediT authorship contribution statement

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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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Appendix A. Supplementary data

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