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A Connected World: System-Level Support Through Biosensors

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Abstract

The goal of protecting the health of future generations is a blueprint for future biosensor design. Systems-level decision support requires that biosensors provide meaningful service to society. In this review, we summarize recent developments in cyber physical systems and biosensors connected with decision support. We identify key processes and practices that may guide the establishment of connections between user needs and biosensor engineering using an informatics approach. We call for data science and decision science to be formally connected with sensor science for understanding system complexity and realizing the ambition of biosensors-as-a-service. This review calls for a focus on quality of service early in the design process as a means to improve the meaningful value of a given biosensor. We close by noting that technology development, including biosensors and decision support systems, is a cautionary tale. The economics of scale govern the success, or failure, of any biosensor system.

1. MOTIVATION

Guided by the United Nations (UN) Sustainable Development Goals (SDGs) (1), many global efforts are converging toward a unifying goal of ensuring a healthy planet that supports future generations. Although the specific aim of each effort varies (see the sidebar titled One Health, EcoHealth, Planetary Health, and International Health Share a Similar Vision), the value systems share common features. Namely, most efforts focus on improving health and promote the need for convergence from many different talent pools. Social systems at all scales are the driver for a connected world. There is much reason to be optimistic that some of the problems we face may benefit from technology-as-a-service. However, for every potential benefit of a techno-fix (particularly at the global scale), there seems to be at least one major pitfall that may deter well-intentioned design. OECD (Organization for Economic Co-operation and Development) nations, often the developers of advanced technologies, comprise only about 20% of the world's population. Economics govern the fate of technology adoption (discussed in Sections 5–7), and unless it is useful to 80% of the global population, the economies of scale may not be applicable.

This review focuses on one specific technology, the analytical biosensor, and the challenges and efforts to develop sensors-as-a-service. Biosensors, and other sensor technologies such as chemosensors, are unique in that data may be produced for any appropriate user who has access, agnostic of the context. When coupled with appropriate decision support systems, biosensors and other analytical tools are uniquely positioned to provide a service to society, allowing users to retrieve information that may not be obviously visible. However, analytical sensors are not immune to the aforementioned technology development challenges, and the question of access (economic and otherwise) may be one of the most pressing at the global scale. In this review, we summarize key advancements in biosensor research, spanning from first principles to ongoing efforts posed to connect sensor data with societal needs. Spanning the chasm between sensor data and societal need is not trivial, and we highlight recent progress that has been made in this journey. We review frameworks and specific tools that may be pillars needed to bridge the gap. In the next section, the evolution of an emerging design concept in biosensing is considered as a starting point.

ONE HEALTH, ECOHEALTH, PLANETARY HEALTH, AND INTERNATIONAL HEALTH SHARE A SIMILAR VISION

The UN SDGs are a blueprint for peace and prosperity for people and the planet into the next generations. The mission of One Health (2), an effort initially led by veterinary medicine societies, is to attain optimal health for people, animals, and the environment. EcoHealth (3), an effort led by the Canadian Health Agency, is similar to One Health but values the health of aggregate systems over individuals within the system. Planetary Health (4), a concept rooted in Norway, is focused more on human health and human social systems than the other two viewpoints, but it still considers animal and ecological health as pillars of the ideology. Two reviews (5, 6) compare the differing views of health and discuss similarities and nuanced differences in these value systems. The International Health Regulations (IHRs) are spearheaded by the World Health Organization (WHO), with more than 195 signatory countries, to build the capability to detect, assess, report, and respond to public health events. The literature describing design concepts rooted in circular economics (7) is intertwined with global health. Taken together, these global efforts are important drivers that contextualize the need for technologies, including biosensors.

2. THE EVOLUTION OF RTA(D)?

Biosensor research and development is extremely diverse and depends on contributions from many academic disciplines and commercial sectors (8). At its core, biosensing is driven by the

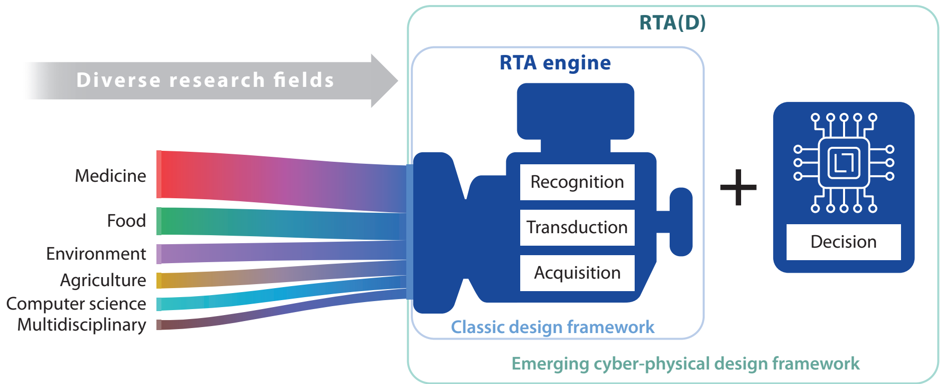

Figure 1

The recognition-transduction-acquisition (RTA) engine is fueled by advancements in numerous disciplines and actuated by data analytics through decision support (D). Understanding biomolecular phenomena is critical for maintaining momentum. The evolution of decision support as a fourth design component may open new doors.

RTA (recognition-transduction-acquisition) engine and is fueled by advancements from numerous research fields. Data analytics (e.g., signal smoothing, data transformation) is pivotal to sensor development in the acquisition (A) component. The emergence of decision support (D) as a fourth component is driven by advancements in data analytics. To visualize this (**Figure 1**), recent reviews on the state of biosensor research (9–13) were mined to create a Sankey diagram that demonstrates the emerging RTA(D) design concept.

Figure 1 illustrates an emerging area of sensor science that is focused on decision support. Conceptually, it is important to add a fourth pillar to the classic RTA framework, rather than lump together decision support and acquisition. The rationale for a fourth design pillar lies in the mathematics. Classic sensor signal processing (e.g., unstructured high-dimension data) is typically limited to the classification of data (e.g., scoring, clustering). Modern techniques such as feature extraction often utilize machine learning (ML) for drawing connections between sensor data and textual (linguistic) data. The difference is subtle, but here we call for this fourth pillar in an attempt to provide focus on outcome (i.e., the user need) and to connect foundational knowledge from decision science with sensor science.

The following subsections briefly highlight a few key contributions, organized using the RTA(D) pillars as guideposts. These and similar efforts, as well as the associated protocols and methodologies, are the foundation of sensing. Without discoveries at the atomistic and human spatial scales, innovation and discovery of new tools are not feasible. Evolution toward systems-level support to serve the connected world is rooted in decision science.

2.1. Key Contributions in the Area of Biorecognition

Key contributions in biorecognition span nucleotide chemistry to protein systems and DNAzymes. We highlight a few examples in this section.

CRISPR-Cas is now being used in biosensor development. Tang et al. (14) reviewed the application CRISPR-Cas for analytical and diagnostic assay development, including biomolecular processes and integration with existing sensor acquisition systems. Wan et al. (15) developed a CRISPR/Cas-based electrochemical biosensor for pathogen screening (avian influenza A). This is an example of convergence using established sensor platforms (carbon screen-printed electrodes) combined with biological engineering (the CRISPR-Cas platform) for ultralow limit of detection.

Since the discovery of SELEX (systematic evolution of ligands by exponential enrichment) by Tuerk & Gold (16) and coining of the nucleic product as aptamer by Ellington & Szostak (17), aptamer research has continued to grow. Sparked by the invention of slow off-rate modified aptamers (SOMAmers) (18) by SomaLogic, modification of the five nucleotide code using phosphoramidite-like reagents as homologs expanded the capabilities of aptamers. Modified aptamers are now used in many areas (e.g., therapeutics, proteomics, pathology, pharmaceuticals). However, modified aptamers as biosensors are still rare (19).

Modified aptamers may be designed using rational (computational) design frameworks for producing novel attributes: chemical synthesis, high affinity for one or more targets, enhanced environmental durability, and others. Molecular origami and nanoelectronics are two fields that directly benefit from modified aptamer research. Efforts to develop modified aptamers include AEGIS (artificially expanded genetic information systems) (20) and others, as detailed in the review by McKenzie et al. (21).

In addition to gene-based biorecognition approaches, key advancements in the area of protein engineering have occurred in the last five years. One particularly exciting area of research focuses on a naturally occurring chemically induced dimerization (CID) approach that couples molecular sensing to actuation (22). The CID system in *Arabidopsis* (PYR1-PP2C) was used to develop an initial library of more than 20 sense-respond nanoactuators. The portability was compared to other biosensor systems [enzyme-linked immunoassay (ELISA), luciferase systems, luminescence, and transcriptional circuits]. Each of the protein sensor/actuator pairs demonstrated limits of detection on the order of picomolar to nanomolar scale for cannabinoid detection. Expanded use of the CID system for other ligand-binding systems, as well as exploring other signal transduction systems, may be extended to explore other targets.

In the area of bioimaging, real-time tracking of the primary plant growth hormone auxin (indole acetic acid) has been elusive. Herud-Sikimić and coworkers (23) developed a protein-based Förster resonance energy transfer (FRET) biosensor that facilitates visualization of auxin dynamics in planta. Importantly, this nano-biosensor has four key properties: (*a*) reversibility while retaining quantitative signal, (*b*) wide operating range, (*c*) ability to target subcellular compartments without the use of gene expression or protein degradation, and (*d*) no use of cross-reacting metabolites. In plant biology, researchers may finally have the ability to unlock mysteries associated with the dynamic behavior of the spatiotemporal complexity of this growth hormone.

Somewhere between nucleic acids and proteins lie recognition materials such as DNAzymes (which follow the discoveries of Altman and Cech that RNA can function as an enzyme) (24). McConnell et al. (25) review this biorecognition material (rational design principles, sensing strategies). The seminal work on the discovery of Z-DNA (26–28) may also contribute future ideas in biorecognition for sensing. In addition, protein mimetic systems such as molecular imprinted polymers (MIPs) have made great strides since the discovery by Polyavov and expanded by Mosbach and Gunter (see 29). Current efforts focused on nano-MIPs are greatly expanding the existing toolkit of recognition materials (30).

2.2. Key Contributions in the Area of Signal Transduction

Transduction in biosensors is a broad field that is constantly growing, worthy of numerous comprehensive reviews. Here, select contributions related to mobile biosensing are highlighted. Mobile biosensing across the food, environmental, agricultural, medical, and public health domains is a key mechanism if the majority of the world is the intended user [see the detailed review by McLamore et al. (9)].

It is worth noting that the six most cited manuscripts (and 8 out of the top 10 most cited) found when searching the key term biosensor in Web of Science are discoveries (31) or reviews

(32) related to nanoplasmonic techniques. This speaks to the importance of techniques such as localized surface plasmon resonance (LSPR), surface-enhanced Raman spectroscopy (SERS), and derivations thereof. Given the popularity of this research area, several review articles in the past five years highlight the advancements and opportunities in plasmonic sensing (31, 33, 34). One key advantage of some plasmonic sensors over other transduction approaches is the portability.

Classic papers on impedance spectroscopy (35) and amperometry (36) still resonate with many ongoing efforts in translation of these ideas for the development of electrochemical sensors. The patent literature contains many examples of devices that may be traced back to these early works (37, 38). In addition to classic electrochemical devices (e.g., ion-selective electrodes), potentiometry has been used extensively for biosensing (39). Photoelectrochemical devices such as light-addressable potentiometric sensors (LAPS) have been used for detection of enzymatic products as well as biomarker detection (40). Dielectric films of MIPs for potentiometric biosensing have recently been applied for detection of mycotoxins (41) and cancer biomarkers (42). Hybrid approaches such as LAPS and MIP-coated electrodes have shown to significantly improve limit of detection and specificity in complex matrices, perhaps opening new doors for potentiometric biosensing.

Some of the most exciting advancements in electrochemical sensing in the last five years are summarized below. Damala et al. (43) developed a compensation approach similar to other self-referencing techniques (44), whereby drift is minimized (on the order of 0.1 mV/min) and stable recordings for up to five days are achievable in river water. This discovery could be pivotal for potentiometric sensors that are plagued by drift issues (such as multivalent ion sensors) and may open doors for the application of onerous ion-selective electrodes given that the approach does not require any specialty equipment. In another key study by the Bakker group, Kraikaew et al. (45) enhanced the constant potential capacitive technique for ion sensing by developing an autonomous switching system. This approach allows measurement in a single solution, avoiding the necessity of a standard reference solution in classic methods. The technique was applied in pooled serum for analyzing sodium levels and demonstrated excellent recovery. A spin off from this same concept led to the development of a self-powered potentiometric sensor with memory (46). Where in classic constant-potential capacitive sensing most users are concerned about deleterious memory effects in the capacitor, this new technique utilizes the memory as a feature of the device. After the charging step, a single potential measurement (across the capacitor) transduces signal that correlates with ion activity during a specified time period. The approach was used to quantify time-resolved pH changes in river water. Taken together, these three key advancements (removing the requirement for surface conditioning, the use of capacitive switching, and self-powering without reliance on triboelectricity) demonstrate an electrochemical platform that is potentially deployable in water systems.

Exciting analytical advancements are underway in the area of magnetic impedance as a transduction mechanism (13) as well as touch screen sensors. Seminal reviews by the Davis group (47) and Wang group (48) describe touch-based systems for biometrics and small-molecule sensing, respectively. Another noteworthy discovery is a new bioelectric transduction system for self-powered human sweat sensing (49).

2.3. Key Contributions in the Area of Signal Acquisition

Signal acquisition and post-measurement analysis are the third pillar of RTA and have undergone major changes in the last five years. Key advancements in the area of multivariate analysis and nonlinear modeling are briefly discussed below. Many of the sensors summarized in this section are not classically defined as biosensors, but they may offer insight, as the techniques are amenable to other sensor systems.

Multivariate analysis is at the heart of many analytical studies such as spectroscopy (50). In biosensing, techniques such as the partial least squares model, Gaussian process regression, and/or artificial neural networks are common for analyzing sensor data (51). In a recent example, Tuan et al. (52) recently demonstrated an algorithmic approach for smart diagnostics. A deep kernel learning model was developed in Python and implemented in a real-time monitoring system. Sensors were used to monitor ions in a lettuce hydroponic nutrient solution. In a similar line of work, wastewater data (unstructured) were analyzed in a cloud-based system using a soft sensor approach by Wu et al. (53). The dissemination of open source code (GitHub) may pave the way for similar studies.

Another area of current interest in the post hoc signal domain is the development of digital proxies (54–56). Digital proxies require real-time sensor data (structured and/or unstructured) that feed a statistically robust in silico model (commonly from the suite of ML tools). Recent work has demonstrated the use of this approach for monitoring flow-through bioreactors, the protocol and code of which are available in an open access form (57, 58). In addition, digital proxies are under development for bioprinting (59) and mammalian cell culture (60), but to date, sensors have not been integrated for near-real-time modeling, as promised by purported digital twins (54).

2.4. Key Contributions in the Area of Decision Support for Sensors

The lateral flow assay (LFA) is the most common example of a device with three-tier decision support (yes/no/inconclusive). Digitization of the data from any biosensor or biodetector allows the exploration of quantitative data (or semiquantitative) (61) and introduces the notion of uncertainty for the user to consider. Advancements in the area of data fusion and decision support systems have primarily focused on algorithm development in healthcare, namely noncontact wireless body sensors (62). These physical sensors collect periodic measures and then coordinate data prior to fusion. New models based on fuzzy set theory (63) may be amenable to data analysis in biosensing. Similar frameworks were used to connect sensors to decision support systems for coastal weather systems (64) or precision agriculture (65).

In an example of ML connected to biosensing, Rong et al. (66) developed a post hoc data analysis approach for impedimetric biosensors based on protein–protein interactions. An unsupervised support vector ML tool was applied for data analysis (in lieu of equivalent circuit analysis). This effort aims to open new pathways toward direct sensor analysis on site to be extended by improved decision support tools. An open source code and tutorial (written in English, Spanish, Portuguese, and Mandarin) were provided in an effort to distribute the baseline tool and promote challenges/advancement of the technique through open source sharing.

While there are limited examples to date that demonstrate biosensors directly connected to decision support, theories of decision support are well established and have been challenged in different levels of uncertainty (67). In a previous review, we illuminated two different model frameworks for connecting biosensor data to decision support (68) and, in a related follow-up review, we addressed economic issues of the sensors with embedded decision support tools (69). As biosensors and other diagnostic tools diversify, user demand for real-time information grows. This societal need creates opportunities to expand traditional biosensor design frameworks by including decision science with the aim of delivering service. Sensor networks based on RTA(D) are becoming mainstream in healthcare and are also beginning to evolve in the food, environmental, and agricultural domains (70). For this to become a reality, a concurrent effort is needed to establish connections between user needs and sensor engineering using an informatics approach.

3. IS BIOSENSOR INFORMATICS ON THE HORIZON?

The notion of biosensors as-a-service to society depends on the fusion of sensor data with other types of metadata (e.g., data from mixed methods social science studies). Agent-based systems facilitate status update based on correlation with new data streams, whether from sensor data or metadata, but these systems have unique requirements in terms of data privacy/security (71). One design feature that can overwhelm any design team working in analytics is the complexity of the molecular phenomena coupled with device physics. If we add the complexity of the user need, this becomes a nebulous mixture of uncertainty (71). Allen & Boulton (72) juxtapose the inevitability of system uncertainty against the impossibility of having full knowledge as a driving force for change. What are the processes and practices for addressing such complexity?

We may begin to unpack the complexity of biosensors-as-a-service to society by extending the classic information hierarchy (73) and extend the model to include tools in the hidden layer that produce data (**Figure 2**). In this model, the boundaries between layers of W-U-K-I-D (wisdom, understanding, knowledge, information, data) are porous. Exchange across the boundaries is dynamic, albeit hierarchical. Data from sensors may transform into useful information through data analytics (68), moving up the hierarchy from the hidden layer to the first actionable layer.

In **Figure 2**, the sensor-data-information foundation represents approximately 70–80% of the system. These so-called Pareto problems (74) are where many opportunities lie for biosensor research. Extending beyond the foundation of data-informed action (i.e., above the information layer) may be unrealistic in the near future. Currently, extension into the knowledge domain may

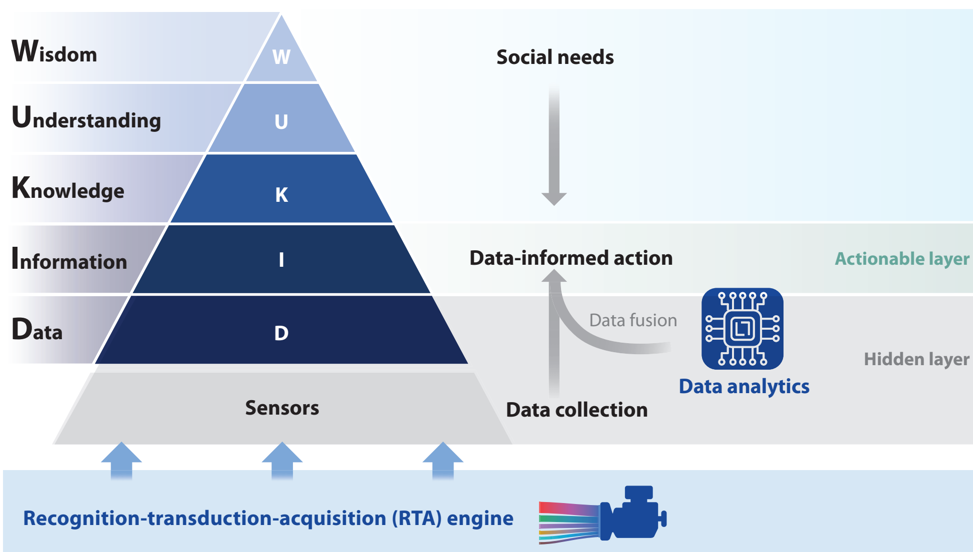

Figure 2

The information hierarchy may be extended to include tools in the hidden layers that produce data, such as sensors. In this model, social needs and data converge in the actionable layers to produce information. The recognition-transduction-acquisition (RTA) engine is the underpinning of data production, but sensors alone are not capable of action. Data analytics is the vehicle for advancing data into the actionable layer (decision support systems, partially autonomous systems that are capable of actuation). In the diagram, the sensor-data-information foundation (*lower three levels*) represents approximately 70–80% of the system, which we argue is where many opportunities lie for biosensor applications. Extending beyond this foundation may be unrealistic in the near future; even extension into the knowledge domain may be a stretch for cyber physical systems.

be a stretch for cyber physical systems (CPSs), as fusion of knowledge networks with sensor data has not been achieved. In the near term, if we discipline our efforts to focus on Pareto problems, we may make important strides. Because key performance indicators (KPIs) reside within the information layer of the hierarchy, we may begin to delineate pathways by connecting sensor KPIs to service-oriented indices.

Meaningful use is a term used as a system metric in healthcare record curation (75, 76), where quality of service (QoS) is the tangible outcome of medical technologies and practices. QoS has been applied in wireless sensor networks applied in the healthcare industry through near-real-time interaction of data using agent-based models (77–80). The dynamic nature of the agent-based system fuses sensor data with metadata on the situational context (a feature referred to as context awareness in the computer science literature). Yet, those QoS indicators are not common design aspects, nor reported outcomes, for biosensor development in the literature. Thus, analytical sensors designed for the Connected World must modify the design approach at the most granular level, considering the nature/ontology of sensor data, as well as contemporary issues of data privacy/security (71). This notion is intertwined with the economic principle of path dependence, as discussed in subsequent sections.

QoS and related indicators are key to connecting sensor data with the information hierarchy shown in **Figure 2** and opening pathways toward decision support. Analytically, the addition of QoS is merely an extension of the mixed methods approaches used in clinical studies. For example, quantitative diagnostic tools often utilize metrics such as the Youden index (81) to report testing efficiency. The mathematical framework for this index is rooted in calculations of percent positive/negative agreement in an analytical context or clinical sensitivity/selectivity in the context of a clinical trial. Calculation of the Youden index, and other similar indices, depends on sensor KPI such as sensitivity and limit of detection. Data for calculating diagnostic indices may be nondigital, such as LFAs (82), or digital data from technologies such as wearable sensors (83). The notion of integrating new indices and metrics related to QoS depends on an informatic backbone, but the idea of informatics for sensors has yet to be established within the general research communities.

Although details are beyond the scope of this review, sensor informatics (SENSICS) requires three key types of data: materials data (e.g., metadata on material stability, toxicity), sensor KPI data (e.g., sensitivity, limit of detection, reversibility in a given application), and user data (e.g., metadata on user needs, QoS metrics). Databases within the materials genome initiative (84), for example, may satisfy the first requirement. However, databases on sensor KPIs and user experience have not yet crystallized. Early efforts toward developing a sensor KPI database are underway (85), but are application-specific and must be applied with caution. Recent advancements in biometrics and touch-based sensing (47–49), as well as the emerging use of smartphones in participatory surveys (86), could produce data for the third requirement. Analytical sensing researchers would benefit from focused efforts on building high-quality data sets for each of these three domains related to SENSICS.

The notion of connecting these three information nodes is a major challenge. The heterogeneity, distribution, and aberrant veracity of the data from users and sensor developers are in sharp contrast to the highly structured field of materials informatics, making integration a difficult proposition. The pieces of the puzzle are known (data on materials, sensors, and users), but the relationship among and within each component remains elusive. Moving forward, these relationships may be explored using knowledge graph theories (87) (see the sidebar titled Graph Theoretic Approaches).

Biosensor data, considered in isolation, are agnostic to change(s) in current status, but interpretation of the data and extraction of meaningful value are not. Agent-based systems are capable of correlating new(er) information with prior information for drawing inference based on established

GRAPH THEORETIC APPROACHES

Graph theoretic approaches are key for search and discovery of data and information, facilitating relational analysis and knowledge discovery. Knowledge graphs are one tool from graph theory and have five key elements: (*a*) an entity may have multiple entity types; (*b*) relationships between a pair, or pairs, of entities have associated labels; (*c*) entities may have more than one interrelationship; (*d*) an entity may possess different values of a single attribute; and (*e*) entity types are defined by a hierarchical ontology (88). Examples applied to material science are emerging. By using relationships between materials and their properties, which may be organized as graphs with edges and nodes, Tshitoyan et al. (89) developed a methodology that may lend itself to exploring non-obvious relationships by noting an entity relationship mode that remains the bread and butter of context awareness. Developing and implementing knowledge graph tools may aid in unleashing new ideas, reveal unknown features, and enable context-aware knowledge discovery.

logic networks. Contextualization of the problem in a given space and time may alter the nature of the need and therefore modify the data integration step prior to feature engineering. This illustrates the need for a robust biosensor KPI database not limited to claims of superior sensitivity and limit of detection. To realize these ambitions, a data warehouse that promotes robust testing of analytical devices in controlled and uncontrolled conditions is required. If such an informatics database is developed using an open science framework, associated repositories may provide the key evidence needed for optimizing QoS from numerous biosensor systems to enact SENSICS.

4. KNOWLEDGE GRAPHS AS A TOOL FOR DECONSTRUCTING COMPLEXITY

Digitization of information is not a new concept. The idea of atoms to bits (A2B) predates the invention of the computer (90). Underneath many of these concepts and metaphors lie graph networks, which are ML paradigms that support relational reasoning and combinatorial generalization. Liu & Sun (91) provide a tutorial review of ML, focusing on the fundamental principles and applications of data classification or clustering, as well as use of ML for in silico models, rational design of biomaterials, or molecular computing. In addition, ML may also play an important role in retroactive analysis, particularly when validating data with ground truth (92).

Knowledge graphs are process-oriented diagrams that show the mechanism for nonhuman computer systems to understand relationships between entities, objects, processes, people, and things (93). Relationships between entities are critical in the context of making decisions and thus necessary to develop biosensors that aim to provide decision support. The resource description framework (RDF) is a general method for description and exchange of graph data based on principles of linguistics (noun, verb, subject, predicate). When data are mapped against an RDF ontology, instances of the data are expressed based on the idea of making statements about resources in the form of triples [using RDF terminology (94)]; see **Figure 3** for an example. RDF triples, despite their shortcomings and potential for linguistic bias, enable the formation between two or more objects by linking a series of relationships but with the distinct disadvantage that knowledge graphs do not address causality. The latter makes knowledge graphs only as useful as the facts as known to the creator (programmer) but without any intelligence whatsoever.

Knowledge graphs are the basis for ideas in ubiquitous connectivity, where networks of knowledge graphs can form the foundation linking objects and things in the context of an internet of things (IoT). IoT is a digital design metaphor that may be viewed as a subset of CPSs. Mayer & Baeumner (70) review potential analytical sensors through 2018 and call for an internet of

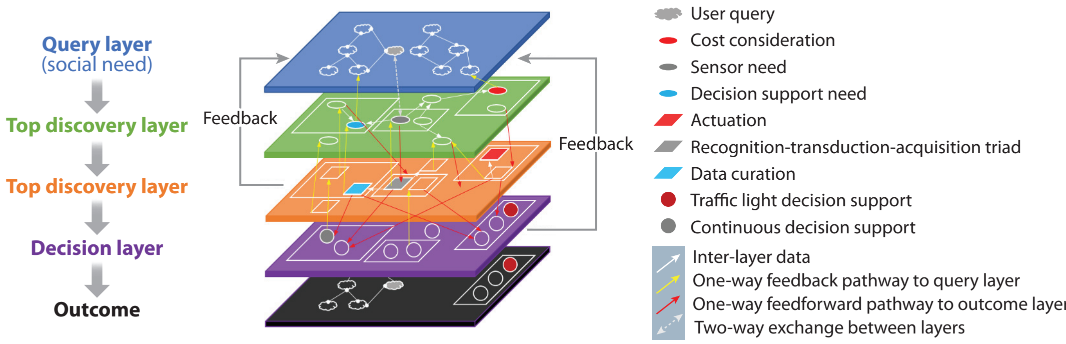

Figure 3

Knowledge network graph illustrating interactions for a single user query and outcome. Individual queries within the query layer (social need) interact and then fuse to a single node that interfaces with the tool discovery layer. Each subsequent layer is composed of multiple components, as shown in the legend. Data and information converge to advance through the layers toward sensing, decision support, and a final outcome. An example is illustrated using nodes, as indicated in the legend. The sensing and decision layers provide multiple types of service based on the initial query, creating feedback that improves quality of service. Upon multiple iterations, this example leads to a testing outcome that is conveyed in response to the query. Figure adapted with permission from Reference 9; copyright 2021 Elsevier.

analytical things for service in the areas of agriculture, food production, and healthcare, among other applications. The acquisition, analysis, and communication of processed data form the basis for an internet of analytical things. In the four years since their review, progress has been made in expanding this concept beyond what we denote below as the sensing and decision layers.

The knowledge network in **Figure 3** illustrates one example for connecting user query with decision support in a biosensing application. The graph network demonstrates an example of relational data that is a service as part of a larger system-of-systems. The sensing layer knowledge graph is the comfort zone for many research labs working in sensor development. In this isolated layer, a problem has been previously contextualized, which is used to inform the design and testing of a biosensor using the RTA framework. KPIs are the outcome of this layer (sensitivity, limit of detection, etc.). To interact with other metrics of the system, analytical outcomes (KPIs) must interface with other layers of the knowledge network. For example, KPIs may interact with QoS in the query layer and decision layer. This illustrates the importance of upstream activities in relation to sensor data (context of the query, tool discovery) and downstream processes (type of decision support requested). Further, feedback loops shown in the diagram illustrate the complex relational analysis.

Examples of recent progress contributing to the framework in **Figure 3** include the development of a proof-of-concept tool discovery layer (85) as well as artificial reasoning tools for control of water pumps (95) or traffic light decision support (96). This knowledge graph diagram provides a single example of a proof-of-principle for a more complex system and is not intended to represent the complexity of analytical and social sciences.

Figure 4 diagrams one conceptual cyber physical decision support system applied for the detection of target(s) called for by current societal needs. In the example, hidden and actionable layers fuse sensor data (**Figures 2** and **3**) via agent-based systems using standards such as the RDF triplet, among numerous others. If integrated with appropriate cybersecurity, the sensor plus decision support system may be capable of carrying out such agent-driven tasks, as depicted in **Figure 4** (71). On first inspection, the approach in the figure may seem intuitive, but for current digital systems, the absence of causal architecture makes it difficult to select what is relevant,

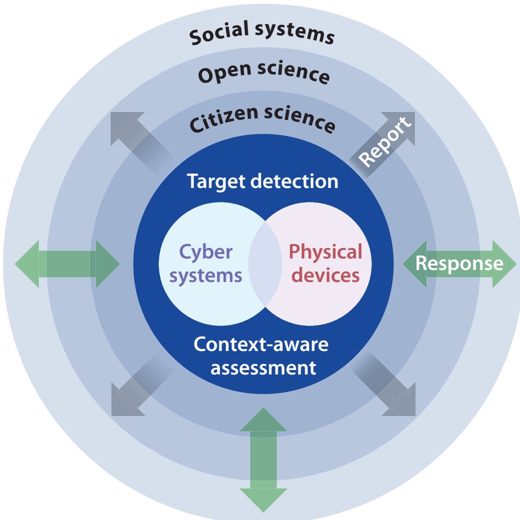

Figure 4

The key driving force for development of a future cyber physical system (CPS, represented by the Venn diagram in the center) may be a focus on ensuring the health and welfare of future generations. Agent-based systems (*two-way arrows*) are key to CPS data fusion, including bidirectional response (*green arrows*) and reporting (*gray arrows*) as shown. Citizen science and open science are pathways and processes that have the potential to connect CPSs with people. The four pillars of the World Health Organization's International Health Regulations are shown in white text. Target detection and context-aware assessment (*innermost circle*) occur within the CPS domain, where reporting and response are integrated into decision support systems based on agent-based systems.

relative to the semantic context, and to connect distributed data with the aim of extracting information that aids decision making or executing action(s). Embedding knowledge systems from the social component (see top of **Figure 2**) is a complex and uncertain task for any CPS (see Sections 5 and 6). This is the rationale for using RDF triples as a poor but only available substitute for knowledge nodes (see the sidebar titled RDF Triples). RDF is a machine-readable standard based on principles of linguistics. Despite the absence of causality and lack of semantics, as well as other shortcomings and the potential for linguistic bias from RDF, graph networks spanning the hidden and actionable layers of the information hierarchy may be viewed as a crude architectural framework formed to link a series of relationships in a manner similar to the example in **Figure 4**.

RDF TRIPLES

The resource description framework (RDF) standard is a general model of entities (nodes) and relationships. When data are mapped against an RDF ontology, instances of the data are expressed based on the idea of making statements about resources in the form of subject–predicate–object expressions. The linguistic application upon which RDF was established is intuitive, albeit incomplete. Interestingly, the RDF ontology is applicable to multi-sensor data as well as the metadata described herein. In this ontology, the subject denotes the object, and the predicate denotes a single semantic trait or aspect of the object that can be a literal value or expressed as a relationship between the subject and another object that is the target of the relationship. See knowledge network graph in **Figure 3** for an example specific to the combination of a user query and a sensor plus decision support system.

Contributions in the area of data analytics, rational design, and molecular computing (91) fuel the development of next-generation systems required for the example process flow (from user query to decision support outcome) shown in **Figures 3** and **4**. Workflows in these diagrams were based on the QUDE (quantifying uncertainty in data exploration) system (97). In the QUDE model, data extraction, integration, and processing from various data sources converge through a feature extraction filter, leading to a knowledge graph network. Feature extraction is key to efficient decision support systems and is paramount for agent-based systems. QUDE tracks uncertainty through the workflow in an attempt to minimize algorithmic bias as system complexity increases.

As reviewed in Sections 2–4, the frameworks and skillsets are in place to propel the field of biosensors toward systems-level support. However, this optimism is a cautionary tale. Technology mistranslation (98, 99) and low adoption, coupled with the known ethical problems of ML (100) and misuse of black box models for high stakes decisions (101), are a few of the obstacles we face for realizing the concept of sensors-as-a-service to society. An overarching question first raised in Section 1 is: Do these technologies deliver a service to meet at least 80% of certain societal needs?

In the next section, we discuss the opportunities and challenges for developing analytical biosensors and decision support systems viewed through the lens of this challenging question.

5. OPPORTUNITIES FOR BIOSENSING-AS-A-SERVICE

The goals of the SDGs and associated global health efforts are a blueprint that could define biosensor research and development. Using biosensors as a boundary object, convergence of the goals listed in the first sidebar may be formalized in the following summary statement: Future biosensors may focus on ensuring the health and welfare of future generations of people, animals, and environment by detection, assessment, reporting, and response. As summarized below, each of the four tasks in this summary statement interact through a CPS (**Figure 4**).

5.1. Opportunities in Analytical Biosensing

One key opportunity for analytical biosensing is the improved understanding of controlled actuation. Actuation of sensor systems requires the design of RTA processes that have more than one state (where the state may be physical and/or cyber). Examples of multistate biosensor systems have been demonstrated. For example, polymer-DNA nanobrush systems that physically actuate were developed for detecting bacteria in food systems (102, 103). In this system, nanobrush hydrogels were actuated using either thermal-responsive or pH-responsive polymers. This was recently extended by integrating a cyber-actuation control system for liquid pumping (connecting macroscale cyber actuation with nanoscale actuation) (96). This system demonstrates the basic ability to partition multistate biosensor signals from the response in combination with partially autonomous actuation of simple control features. In another example of multistate systems to build from, de novo protein switches have been developed as biosensors (104). The aim of this approach is also to auto-actuate, but this new biosensor system has room to grow in terms of sensitivity and repeatability. Realization of multistate actuating systems, in whatever modality, may improve testing accuracy by minimizing false positives/false negatives (i.e., improving the Youden index) (105). If actuating systems are improved in a manner that allows us to partition signals with tight control of material-scale actuation, we may improve our understanding of RTA causality (71) when testing complex media.

Development of actuating biosensors using mature technology platforms may expedite the development of systems that possess detection, assessment, reporting, and response features. Use of mature platforms improves the likelihood that developed sensor systems are amenable to use in centralized analytical facilities and as decentralized applications (e.g., point of care, point of need, point of use). Example platforms include wearables, screen-printed electrodes, cage systems such as metal-organic frameworks (MOFs), and laser-induced graphene (LIG) devices. Numerous reviews detail the current state-of-the-art for wearables applied in biosensing (106, 107), including self-powered devices (108) and biosensors that are used in theranostic applications (109). Singh et al. (110) recently reviewed the market status of screen-printed electrodes (including multilayered inks and nanomodifiers). Both wearable biosensors and screen-printed bioelectronics/biosensors will likely continue to grow in the future, as discussed in recent reviews.

Chemical cages such as MOFs may become potentially transformative as a biosensor platform to trap/release molecules on demand (111). This multistate platform is amenable to hybridization with biomaterials including aptamers, peptides, and other biomacromolecules (112, 113). A similar material, deemed nanocontainers, is a polymeric structure that combines some attributes of MIPs and MOFs as a multistate platform (114). One theoretical advantage of multistate platforms in point-of-use sensor systems is the ability to differentiate between false positives and false negatives. Using a two-sensor system with two states fortifies the result (outcome). For example, the hACE2 SARS-CoV-2 biosensor may test positive for spike protein in saliva, as demonstrated by Moreira et al. (115). If this biosensor were expanded to be used in a multiplexing format together with a lectin biosensor for the spike glycoprotein, a negative test may be observed due to the presence of a glycan shield. Using such a multiplex/multistate approach, the probability of a false positive would be higher. If both sensors were positive [spike(+); glycan(+)], then the credibility of the positive result would be much higher (nonzero probability of a false positive) and vice versa. It is worthy of future research to explore whether one could add/subtract molecules in the same testing microenvironment using MOFs, nanocontainers, or as demonstrated in the microRNA vaccine, lipid micelles. This raises the questions of whether chemical cages or molecular Hoberman spheres could enable differential molecular diagnostic tools/devices to enhance strength of decision support systems at the point of use. There is much opportunity in creatively transforming principles into practice based on the fundamental disciplines of analytical chemistry.

Since its discovery nearly 10 years ago (116), LIG has quickly become a competitive/mature platform for biosensing. LIG is amenable to printing using laboratory-grade laser equipment (117) or low-cost laser equipment (118, 119). One important feature of LIG is the ability to directly print/embed microfluidics during fabrication (120) or use single transfer techniques (121). The platform has been used for a multitude of diverse biosensing applications, including aptasensors for small molecules and proteins (122, 123), impedimetric or capacitive biosensors for pathogens (115, 124), cell electrophysiology (125), amperometric biosensing for small molecules (119, 126), and multiplexing devices (127), for example. Numerous protocols are available for the reliable manufacture of LIG electrodes (117, 128). This platform is currently being extended to include actuating systems in addition to many other biosensor systems.

In addition to advances in control systems, the type of material selected for a study is equally important. If preservation of a system for future generations is a goal, the use of sustainable materials for technology development is a key requirement. The basic requirements for development of a technology using sustainable material are well known (129), but as Kirchherr (130) notes, many of the published works on the topic of sustainability may detract from the goal of the SDGs and related efforts. Rather than advocate for a single material in this review, we instead note that the use of sustainable materials and techniques in the development of any technology is a design choice, not a post facto feature. The peer reviewed literature on this topic is growing rapidly, as reviewed recently (131, 132).

5.2. Opportunities for Decision Sciences

Building from the previous section, some key opportunities in decision science related to biosensing are proposed here. We highlight opportunities in informatics and tool development, frameworks for connecting sensor data with decision support, and the inclusion of uncertainty in decision support.

Use of ML in material informatics (133) is now a commonplace approach for in silico models that facilitate rapid predictions of material behavior (particularly for observed behaviors that are difficult to quantify experimentally). For example, Jensen & Lewinski (134) used ML descriptors to identify candidate green materials for nanoparticle synthesis within the guidelines of holistic sustainability assessment. Section 3 introduced SENSICS as a new area of growing interest/need for developing sensors-as-a-service. Key opportunities that may be accomplished in the near term include development of a connected (*a*) open source data glossary, (*b*) repository of biosensor KPIs, and (*c*) tool discovery protocols. First, the biosensing community has in place an open source data glossary that was updated in 2019 (135), but the research community interested in coupling sensors with decision support would benefit from an updated list and access to the repository through open science protocols so that tool discovery procedures may interface with a standard (unifying) data glossary. Second, biosensor researchers lack an open source database where common data elements such as KPIs are stored and available for analysis by the data science community. For example, open access databases such as the RADx-rad data coordinating center managed by the US National Institutes of Health developed such a database for collecting data on research projects focused on rapid diagnosis of COVID-19. This database collects KPIs from more than one dozen biosensor projects that contribute to developing the data dictionary. If similar (application-specific) biosensor KPI databases were established, data-informed trends could be established by mining the publicly available data. Third, protocols that aim to match user questions (i.e., societal need) with biosensor capabilities are emerging (94). Tools such as this complement commercial efforts by identifying users that may benefit from services available in local educational institutions (e.g., agricultural extension services in the United States or other similar institutional service programs). Early proof-of-concept in tool discovery has been established (85), but there is much opportunity to advance the work and integrate feedback loops between users, tool designers, and sensor data. For each of these three opportunities, open science principles are in place to govern many aspects of such an approach (see next section). These ideas depend on a few key steps that would benefit from input from the larger biosensor community working together (perhaps across existing scientific societies).

Working at the interface of the hidden layer and actionable layer shown in **Figure 2** may also be achievable in the near term. At a minimum, three-tier decision support (yes/no/inconclusive) should be the testing outcome of all CPSs, regardless of the type and veracity of sensor data. LFA, the point-of-need biosensor that dominates the current market (136), contains this type of decision support in a visual output. In most cases, LFAs are standard for point-of-need biosensors, where polymerase chain reaction is the gold standard for comparison of analytical performance. The decision support provided by LFAs is a baseline level of decision support for new biosensor systems. For some problems, quantitative data and advanced decision support systems are required. In this instance, decision systems that address uncertainty of testing outcome are a key opportunity for research (e.g., agent-based systems) (68). Development of connected architecture for linking data nodes shown in **Figure 3** has been published in the academic literature (94) but needs to be field tested and challenged under dynamic conditions while considering uncertainty.

5.3. Systems-Level Opportunities

Citizen science and open science are pathways and processes that have the potential to connect technology with people (**Figure 4**). If communication with social systems is a goal, this is a key avenue by which the connection may be realized. Although the two are tightly intertwined, the purpose of separating the discussion is to focus on the outcome. In this review, citizen science focuses on the activities that nonexperts conduct as a component of the biosensor research and development pipeline (from ideation to sampling and data collection/analysis). Open science, as discussed here, is broader in scope and may or may not include the participatory action of citizen scientists.

Citizen science is an opportunity that can expand the user pool by establishing decentralized analytical testing/diagnostic activities which augment the standard testing. One successful approach in citizen science is based on voluntary sample donation (137). Another angle on citizen science is to consider engaging active participants in the sampling, testing, and data analysis pipeline using a more active approach (138). Engaging citizen scientists in the analytical pipeline process has been successful in ecology, marine sciences, and environmental studies (139–144), but it comes with challenges in terms of data privacy and willingness to share data. Further upstream, engaging users in the development of biosensors may resolve some potential unseen problems, as shown by the Citizen Sensing project (145).

Although there is much interest in open science efforts (including citizen science), trust networks between scientists and citizen scientists are lacking. There is a great opportunity for research efforts aimed at these trust networks as well as the interaction among testbed networks that span medicine, food, agriculture, and the environment. For improving sensor data veracity, frameworks for open science protocols could be used. Existing frameworks have been established in cancer biology (146) and social psychology (147), among other examples. Confidence assessment is a growing research area in open science (137) and may drive development of biosensor-specific efforts, if connected with KPIs and QoS. Another opportunity in the area of biosensor data veracity is early engagement with peer review (whether by experts or nonexperts), which is known to improve translation of scientific findings (148). Examples of open science that are relevant to biosensors include the open-source platform Fiji (149), GAMESS (general atomic and molecular structure system) (150), and simple tools such as the multilanguage data analysis tutorial by Rong et al. (66), currently being used by citizen science to process biosensor data in the field.

Biosensors that are designed as a service to society may be disruptive in today's technology market. Seminal papers by David (151, 152) are the foundational work in economics reminding us that technology developers must question whether path dependence is driving research. Path dependence states that early design decisions constrain later events such as sensor capabilities/performance in a non-reversible manner. If technology markets have a tendency toward monopoly (153), the field of biosensors is in need of disruptive approaches. Designing for high value to stakeholder(s) early in the design process is the most logical mechanism to avoid path dependence and ensure devices contribute toward the goals of the SDGs or other related efforts such as the IHRs. Establishing a specific definition of meaningful use (75, 76, 154) in the context of the specific problem may be one place to initiate the design, rather than including these economic and social aspect as an afterthought during marketing. Use of informatics approaches to connect design intention(s) to user need through a KPI-QoS pipeline may be a first step toward biosensors-as-a-service for a connected world.

6. SUMMARY OF CHALLENGES

We highlight major challenges in each of the categories defined and contextualized in the previous sections. Additional references are provided when appropriate.

In analytical science, these challenges include (*a*) maintaining KPIs (e.g., high analytical sensitivity) while also using non-toxic materials, as reviewed by Wongkaew et al. (155); (*b*) the ability to partition signals in complex a matrix; and (*c*) digital biosensors that compete with LFA and/or nucleic acid amplification in diagnostic trials.

In decision science, the challenges are (*a*) causal architectures that connect distributed data to extract information from sensor(s) and social component(s), (*b*) development of a sensor informatics (SENSICS) ontology that supports data from various sources (materials, sensor KPIs, user data), and (*c*) including data storage (144, 156) and privacy.

On a systems level, the challenges are (*a*) establishing a unifying framework for ensuring meaningful use of biosensor data-as-a-service by international communities such as the International Union of Pure and Applied Chemistry, (*b*) breaking the path dependence of biosensors through disruptive approaches, and (*c*) establishing trust networks within analytical testbeds that span medicine, food, agriculture, and the environment (i.e., One Health).

7. CLOSING THOUGHTS

The UN's SDGs, WHO's IHRs, and related efforts are a blueprint for the future design of biosensors aiming to protect the health of future generations. Connecting many devices through a unifying platform may provide the foundation for a connected biosensor world. Granular research on biomolecular mechanisms and/or signal transduction is the foundation for acquiring data, and decision science applied to biosensor data is an emerging research space for pragmatic use. Data from sensors will continue to evolve based on the nature of use cases. This is, justifiably, the key focus of the user community. Sensor data and the information from such data must provide actionable value for the end user. This view is important for the implementation and adoption of biosensor systems but incomplete in terms of what we can learn about the systems that the sensors are probing.

Key questions will drive the future of the research field. For example, identifying one patient with a biosensor for the likely presence/absence of SARS-CoV-2 delivers a solution for that instance, that individual, and that diagnosis. When viewed collectively, these data are crucial to understanding the spread of disease and transmissibility and demographics of the infection. The collective view (epidemiology) is a higher level of analysis that can help a greater number of people. The future of biosensor data science needs an epidemiological perspective. With the increasing volume of data, it is likely that certain structures of data may begin to emerge. Lowest common denominators describing a given application (metadata) may facilitate emerging frameworks for complex systems (such as environmental sustainability) to obtain a higher level view of the field (157). Along these lines, the biosensor community may benefit from considering not only analytical performance metrics but also how data contribute to produce information related to (*a*) the incidence (i.e., unique sample) from which data are extracted, (*b*) the distribution of this incident in a larger population of samples, and (*c*) possible remedy/control strategies that result from the information (see **Figures 2** and **3**).

To meet the need outlined in Section 1, we must ask: Are these technologies useful for 80% of the world? An epidemiological perspective may be a foundation upon which to build next-generation technologies, but an economics of scale is critical if the analytical solutions are to have societal value. Seminal papers by David (151, 152) are the foundational work in economics reminding us that technology developers must question whether path dependence is driving research. If technology markets have a tendency toward monopoly (153), the field of biosensors is in need of disruptive approaches to contribute toward the goals of the SDGs, IHRs and related efforts. Devices that are designed ab initio as a service to society may be that disruptive approach in today's technology market. The specific definition of meaningful use (75, 76, 154) in the context of the unique challenge may be one place to initiate design for meaningful use, and efforts to contextualize the problem(s) with linguistics and computer science may play a role. Connecting designer intentions to user need(s) through a KPI-QoS pipeline via sensor informatics may be a first step toward biosensors-as-a-service for a connected world.

SUMMARY POINTS

1. Goals aimed at protecting the health of future generations (e.g., UN Sustainable Development Goals, International Health Regulations, One Health) may serve as a blueprint for future biosensor design.
2. Integration of societal needs into the biosensor design framework is paramount for achieving biosensors-as-a-service.
3. Sensor informatics (SENSICS) is an emerging concept that may facilitate information arbitrage and optimize design of cyber physical systems that aim to connect societal needs with data-informed action.
4. Data science and decision science should be connected with sensor science early in the design process, rather than after the analytical device is developed.
5. Agent-based systems are key to fusion of sensor data with other metadata, including bidirectional response and reporting.
6. Key opportunities and challenges were identified in three areas: analytical sciences, decision science, and systems-level interactions.
7. Biosensor testing modalities are expanding to include decentralized approaches, which may dovetail with best practices in open science for achieving success at a large scale.

FUTURE ISSUES

1. A future review should focus on the four-way nexus where computer science, statistics, probability, and information theory converge.
2. The field would benefit from a review that highlights and champions analytical technologies (e.g., biosensors) geared toward non-OECD nations.
3. A review should focus on data science advances for sensor data acquisition and decision support (e.g., agent-based systems for biosensors).
4. An issue that explores the societal value of sensor analytics as a point solution (i.e., disconnected, stand-alone output such as a lateral flow assay) is needed. Along these lines, the issue could also explore the value of aggregated data when viewed as a swarm of events.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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