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The Optoelectronic Nose

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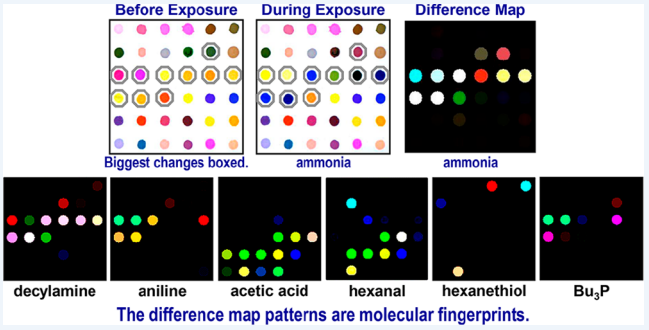
Cite This: *Acc. Chem. Res.* 2021, 54, 950−960 Read Online

CONSPECTUS: How does one tell the difference between one molecule or mixture of molecules from another? Chemical sensing seeks to probe physical or chemical properties of molecular or ionic species (i.e., analytes) and transform that information into a useful and distinguishable output. The olfactory system of animals is the prototype of chemical sensing. Even for human beings (who are generally more visual than olfactory creatures), the sense of smell is one of our most basic capabilities, and we can discriminate among many thousands, and possibly even billions, of different odors. The chemical specificity of the olfactory system does not come from specific receptors for specific analytes (i.e., the traditional lock-and-key model of enzyme−substrate interactions), but rather olfaction uses pattern recognition of the combined responses of several hundred olfactory receptors.



In analogy to olfaction, colorimetric sensor arrays provide high dimensional data from the color changes of chemically responsive colorants as they are exposed to analytes. These colorants include pH responsive dyes, Lewis acid/base indicators, redox dyes, vapochromics, and surface-modified silver nanoparticles. The color difference maps so created provide chemical sensing with high sensitivity (often down to ppb levels), impressive discrimination among very similar analytes, and exquisite fingerprinting of extremely similar mixtures over a wide range of analyte types, both in the gas and liquid phases. Such colorimetric arrays probe a wide range of the chemical reactivity of analytes, rather than the limited dimensionality of physical properties (e.g., mass) or physisorption (e.g., traditional electronic noses). Our sensor arrays are disposable and simple to produce by either inkjet or robotic dip-pen printing onto the surface of porous polymer membranes or even paper.

Design of both sensor arrays and optical readers for their analysis has advanced to a fully self-contained pocket-sized instrument, the optoelectronic nose. Quantitative analysis requires appropriate chemometric methods for pattern recognition of data with inherently high dimensionality, e.g., hierarchical cluster analysis and support vector machines. A wide range of applications for the colorimetric sensor arrays has been developed, including personal dosimetry of toxic industrial chemicals, detection of explosives or fire accelerants, monitoring pollutants for artwork and cultural heritage preservation, quality control of foods and beverages, rapid identification of bacteria and fungi, and detection of disease biomarkers in breath or urine. The development of portable, high-accuracy instrumentation using standard imaging devices with the capability of onboard, real-time analysis has had substantial progress and increasingly meets the expectations for real-world use.

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Received: October 16, 2020
Published: December 17, 2020

https://dx.doi.org/10.1021/acs.accounts.0c00671
Acc. Chem. Res. 2021, 54, 950−960

and used for rapid, real-time discrimination of liquors based on vapor analysis.[3]

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1. INTRODUCTION TO CHEMICAL SENSING

We live in a chemical world: the air we breathe, the liquids we drink, everything we see, touch, or smell. As the world moves toward increased industrial development, the need for new chemical sensing technology becomes critical for innumerable real-world applications. Chemical sensing aims to measure the chemical environment (ranging from the concentration of a single analyte to an overall compositional analysis) as an analytically useful output.[5−8] The biological prototype of chemical sensing is the olfactory system of animals.[9] Humans are more visual than olfactory creatures, but even we are still capable of discriminating 10^4−10^{12} different odorants.[10] The specificity of the olfactory system arises from the pattern recognition of combined responses of many hundreds of olfactory receptors, rather than specific lock and key, host−guest interactions of specific receptors for specific analytes. Taking advantage of high sensitivity and cross-reactivity, it is believed that the olfactory receptors may often be metalloproteins that interact effectively with scent molecules through ligand−metal coordination.[11,12]

By analogy, array-based sensing technology (e.g., electronic noses or tongues) in principle may provide olfactory-like responses for various odorants. "E-noses" have been investigated for nearly 40 years, but they have made only limited penetration into either industrial or academic laboratories.[5,13,14] There are four dirty little secrets about e-noses that are responsible for this lack of success: (1) During exposure to any chemical environment, sensor aging and response drift is inevitable,[7,8,15,16] and this is a horrific problem for library-based pattern recognition because the library rapidly becomes obsolete. (2) Water vapor is also a potential analyte, and humidity changes by thousands of ppm on a daily basis. If one wishes to detect sub-ppm concentrations of VOCs, response to humidity changes is highly problematic.[5,13] (3) Sensitivity is often limited to 100s of ppm because the primary analyte−sensor interaction is physical adsorption.[5] (4) The chemometric data resulting from these traditional electronic noses is actually of very low dimensionality, *regardless of the number of sensors*, and insufficient to discriminate accurately among similar analytes.[5,13,17] In addition, for any pattern-based approach, changes in background odorants (e.g., choice of bacterial culture media) will require reacquisition of analyte libraries.

To overcome these limitations, we have paid very special attention to the design and underlying nature of the interactions of the sensors with potential analytes. First, one must *decouple* the sensors from the electronics to enable the use of *disposable* sensors. In this fashion, the library for pattern recognition no longer needs to cope with sensor aging. Second, one must create sensors in a hydrophobic environment to minimize response to humidity. Third, one must probe a wide range of chemical properties and reactivities whose analyte interactions are much stronger and much more diverse than just physisorption. Physical adsorption/absorption will dominate any interaction of analytes with simple surfaces (e.g., metal oxide sensors, chemFETs), low dimensional nanomaterials (e.g., nanotubes, nanowires, graphene), or polymer coatings (e.g., coated quartz microbalances, conductive polymer sensors, etc.). The primary contributions to physisorption (van der Waals, weak hydrogen bonding, polar interactions) are roughly equivalent to what chemists refer to as "hydrophobicity", and in general with such devices, a single dimension is overwhelmingly dominant and contains >90% of the total variance among analytes.

Chemical property space, however, has a very high dimensionality because of the large number of reactivities that are largely orthogonal to one another (e.g., Lewis acid/base, Brønsted acid/base, redox, electrophilicity, nucleophilicity, hydrogen bonding, polarity, etc.). To differentiate among the broad range of volatile compounds and the possible mixtures thereof requires high-dimensional data representing the extreme diversity of chemical properties space. This is why the olfactory system uses hundreds of receptors. Chemically diverse arrays solve both the third and fourth problems: stronger interactions resulting in greater sensitivity (and with disposable arrays, "poisoning" of the arrays is no longer problematic), and diverse interactions dramatically improve the arrays' discriminatory power (from the resulting high dimensionality of the array data).

We examine here our colorimetric sensor arrays and their analyses, which overcome many of the weaknesses of prior electronic nose approaches. These arrays, made from diverse chemically responsive colorants, produce a composite pattern of color changes that reports the local chemical environment; i.e., they produce a unique molecular "fingerprint" for any given analyte or mixture of analytes.[17,18] The arrays and their analyses have been commonly referred to as *optoelectronic* noses or tongues.[13,17,19,20] We primarily review our most recent progress on trace detection of toxic volatile compounds and demonstrate applications in food inspection and biomedical analysis. In addition, we highlight our recent efforts on cumulative, dosimetric sensor arrays that greatly improve sensing properties and create new classes of applications for monitoring of cultural heritage objects and museum microenvironments.

2. COLORIMETRIC SENSOR ARRAYS

2.1. Intermolecular Interactions

Chemical sensing is, ultimately, molecular recognition, and molecular recognition derives directly from intermolecular interactions.[13] The strength of interaction (i.e., change in enthalpy) among the various intermolecular interactions has a continuous range from the weakest and least specific (~5−10 kJ/mol), e.g., van der Waals and dipole interactions, to hydrogen and halogen bonding, to charge-transfer and π−π molecular complexation, to electrostatic ion−ion and proton acid−base interactions, to the strongest of covalent or ionic ligation and bonding (~50−1100 kJ/mol).

For colorimetric sensors, two structural features are essential to the design of the molecular structure: functionality to chemically interact with analytes, and a chromophore to couple with that interaction. In many ways, colorimetric sensor arrays revisit the earlier, pre-electronic era of analytical chemistry (e.g., pH, complexometric, and redox indicators),[21] quantified by the addition of modern digital imaging and pattern recognition techniques.

https://dx.doi.org/10.1021/acs.accounts.0c00671
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2.2. Classes of Colorimetric Sensors

Based on the specific chemical interactions involved, the chemoresponsive optical sensors can be divided into two classes: (i) reversible sensors and (ii) dosimetric (cumulative) sensors. A linearized sensor array[22] incorporating a diverse set of 40 reversible or dosimetric dyes is shown in Figure 1. In both

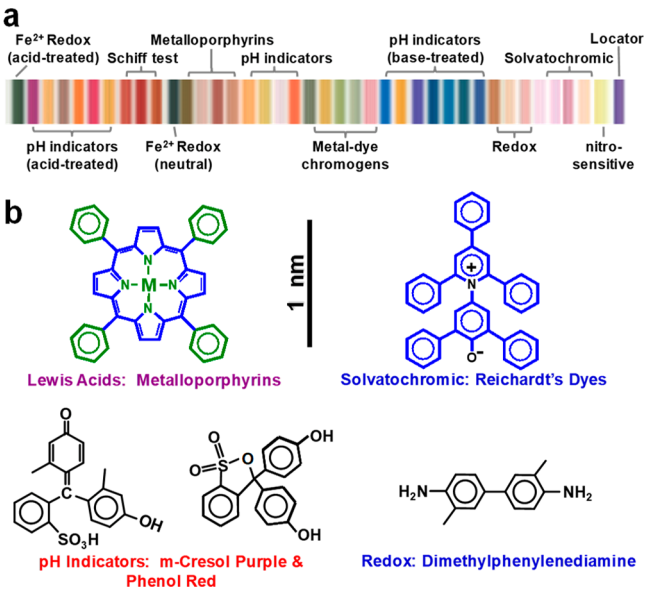

Figure 1. Constituents of the colorimetric sensor array for explosive detection. (a) A 40-element linearized colorimetric sensor array that incorporates a wide range of chemoresponsive dyes, both reversible and cumulative. (b) Structures of examples of Lewis acid dyes, solvatochromic dyes, pH indicators, and redox indicators. Adapted with permission from ref 17. Copyright 2019 ACS.

classes, the sensor arrays are considered disposable and before use are typically stored in aluminized mylar pouches under N_2 to avoid contamination or photochemical degradation.

2.2.1. Reversible Sensor Arrays. Reversible sensors involve interactions of analytes with dyes that are in equilibria and generate observable color changes, including Brønsted acid/base indicators,[21] Lewis acid/base dyes (including metalloporphyrins),[18,23−25] and vapochromic/solvatochromic dyes[26] (e.g., responsive to local polarity; typically an extended π-system with an electron donor at one end and an electron acceptor at the other, such as merocyanines).

Our earliest versions of colorimetric sensor arrays were composed of metalloporphyrins (as mimics of olfactory receptors), which rely on Lewis interactions for the recognition of various ligands by the metal ion.[18] With the exploration of a broader collection of chemoresponsive colorants, the variety of optical sensors and categories of chemical interactions (as mentioned earlier) has been substantially extended,[27] and structural modification of metalloporphyrins to provide shape-selective steric differentiation of analytes has also been demonstrated.[23,28]

The ready availability of precise and inexpensive digital imaging permits facile measurement of color changes in these colorimetric sensors. As shown in Figure 2a, images of an array before and during exposure to analytes permits the quantitative comparison using a difference map created simply by taking red values minus red values, green minus green, and blue minus blue.

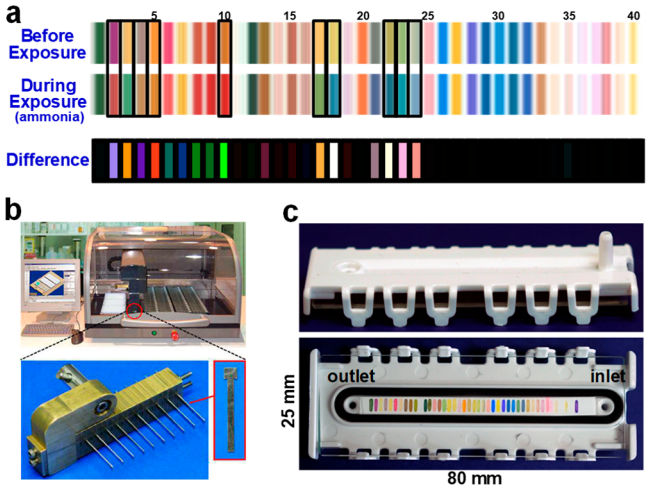

Figure 2. Fabrication of the linearized colorimetric sensor array. (a) Examples of images of the 40-element sensor array before and after exposure to ammonia at 1 ppm and the resulting color difference map. (b) Array printer and bar-shaped print head. (c) Cartridge packing of the array for gas sensing; dead volume is <50 μL. Adapted with permission from ref 22. Copyright 2016 Royal Society of Chemistry.

A related class of reversible sensors are displacement assays that use a natural or artificial receptor already bound to a chromophore or fluorophore and competitive binding of the analyte with release of the chromophore or fluorophore.[29,30] A potential shortcoming of displacement strategies, however, is the diminished sensitivity of the assay due to the binding competition.

2.2.2. Dosimetric Sensor Arrays. Dosimetric sensors involve irreversible (and therefore cumulative) chemical reactions, including redox dyes,[31] chromogenic precipitating[32] or aggregative indicators,[33] and plasmonic nanoparticles.[4,34,35] In addition, the design of matrixes or supports holding those dyes also plays an important role in the improvement of their chemical selectivity by providing analyte access to the chromophore or by modifying the local environment of the chromophore.

For some applications, particularly in ultratrace detection (ppb and below), the development of cumulative or dosimetric sensors is desirable. The use of optical responses from irreversible physical agglomeration of antibody-coated nanostructured materials has drawn massive attention in recent years for biomolecular sensing.[36]

Of special interest to us for small molecule sensing, chemical sintering has recently been shown for aggregation of silver nanoparticles, and a new class of sensor arrays for ultrasensitive detection of reactive gases was demonstrated.[4,34,37] Inspired by the well-known sintering of metal catalysts under reactive conditions, we designed a sensor array with printed Ag nanoparticle inks for dosimetric monitoring of trace concentrations of reactive gases at ambient conditions.[4] Chemically induced nanoparticle sintering leads to changes in the localized surface plasmon resonance, and consequently the color, upon exposure to reactive volatiles (Figure 3a, b). The cumulative nanoparticle sensors generally show detection limits of sub-ppb levels for air pollutants such as SO_2, NO_2, HCOOH, and HCHO for 1 h exposures (Figure 3c). The sensor array is impressively unresponsive to other environmental factors that may severely interfere, including humidity variations or CO_2 concentrations.

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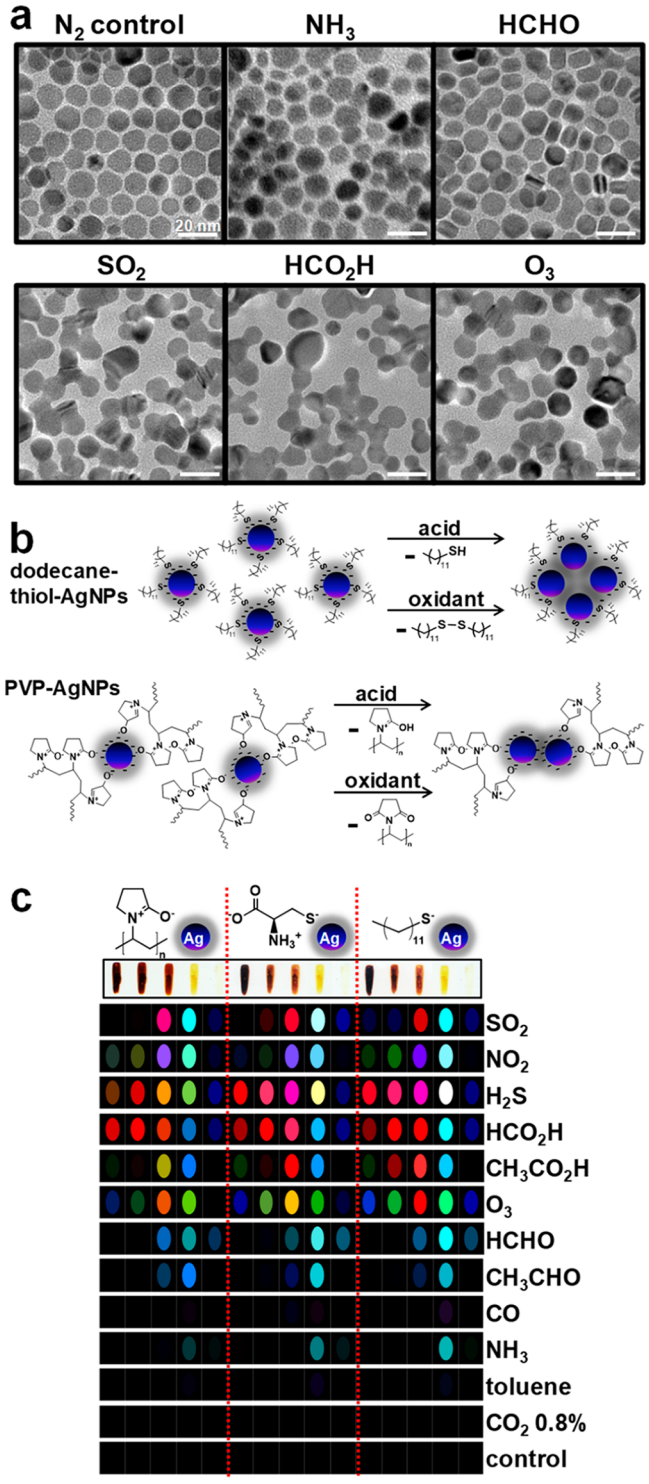

Figure 3. Illustration of sintering-induced color changes with a silver nanoparticle (AgNP) array after exposure to different gases. (a) TEM micrographs of drop-cast AgNP inks dried and then exposed for 10 min to N_2 (control) and to 1 ppm of analytes. (b) Proposed agglomeration mechanism; in the presence of acids or oxidants, capping agents are removed, and nanoparticle sintering occurs. (c) Difference maps of the color changes of the array to 11 gas species at 1 ppm, CO_2 at 8000 ppm, and a clean-air control, all at 50% relative humidity. Adapted with permission from ref 4. Copyright 2019 Wiley.

3. SENSOR FABRICATION AND INSTRUMENTATION

3.1. Array Fabrication: Printing and Substrates

For color changes to occur, analytes must have access to the chemically responsive colorants. The matrix in which dye molecules are immobilized and the substrate upon which the ink formulations are deposited will both contribute to the efficacy of the sensor array. Chemically inert, hydrophobic host matrixes improve sensors' chemical stability, sensitivity, and selectivity.[38] Substrate and matrix surface functionality, hydrophobicity, and porosity can be readily adjusted. In addition, the matrix can also create a sterically confining surrounding to introduce shape selectivity, e.g., molecularly imprinted polymers (MIPs).[39]

Various methods, including spin-coating, inkjet, and microarray pin printing have been used to prepare optical sensors on different solid supports. Most notably, a robotic dip-pen printing method was developed to produce colorimetric sensor arrays with square or linear geometry on a wide range of substrates, e.g. reverse phase silica, acid-free paper, and porous polymer membranes.[40]

The use of hydrophobic materials as matrixes, substrates, and dye choices, for example, greatly diminishes sensitivity to variations in ambient humidity. For example, we reported dye formulations using organically modified silicates (ormosils) that display well-defined nanopore structures (<100 nm diameter);[41,42] the presence of nanostructured porosity facilitates the mass transport process and accounts for fast response times (<1 min) and sub-ppm sensitivity for a varied set of toxic industrial gases.[38,43]

A near ideal colorimetric sensor array is shown in Figure 2: the linear arrangement of the sensors in the array minimizes dead volume (Figure 2c), and a chemically diverse selection of chemoresponsive dyes is immobilized in either plasticized or nanoporous ormosil formulations deposited on a porous polypropylene membrane (Figure 2).[44,45]

In general, as the component size is decreased for the chemically responsive sensor, the response time and the sensitivity increase for the resulting sensor arrays. Large surface-to-volume ratio and resultant high surface energy of nanoparticles are impressively beneficial to sub-ppb recognition of reactive volatiles, as illustrated in Figure 4.[4]

We must also mention the clever use of fiber optic bundles as a separate class of optical arrays developed by Walt.[8,46,47] These are important fluorescent array detectors (in which end-etched optical fibers are encoded with fluorophores on microspheres held at the end of the fiber bundle) for the measurement of biologically important analytes.

3.2. Instrumentation: Digital Imaging of Sensor Arrays

Array-based colorimetric sensing requires measurement of the color changes of each of the array's sensors. The sensor array is digitally imaged before and during analyte exposure, and a color difference profile is generated in real time by subtracting the before-exposure image from images during analyte gas exposure (Figure 2a). This pattern is then compared to a library of color change patterns previously obtained from known analytes at known concentrations. The patterns obtained by digital color imaging are well-represented as 3N vectors of red-green-blue differences, where N is the number of sensor spots. These libraries are extremely compact, require little memory storage, and are easily updated.

Recent advances in digital imaging technology have provided numerous choices of tools for recording optical responses, including digital cameras, flatbed scanners, and even cell

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Acc. Chem. Res. 2021, 54, 950−960

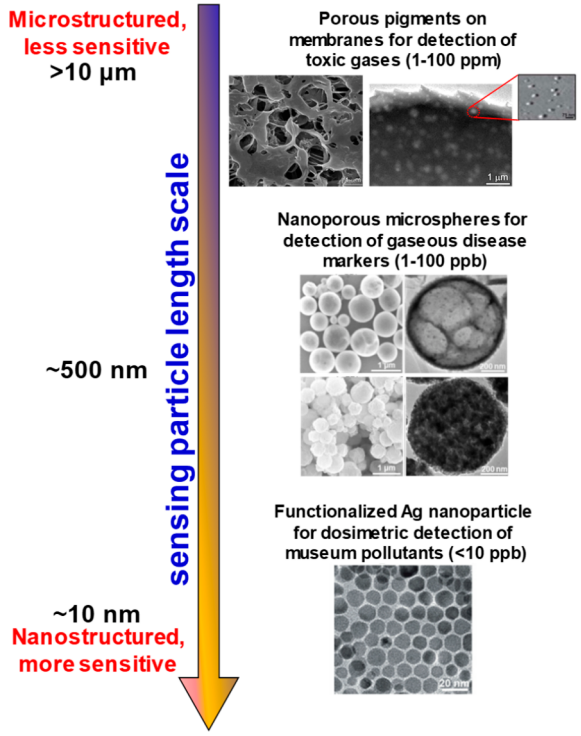

Figure 4. Correlation between the sensor micro/nanostructure and detection sensitivities. Micrographs reproduced with permission from refs 38, 48, and 4. Copyright 2011 Royal Society of Chemistry, 2018 ACS, and 2019 ACS, respectively.

phones.[17] We developed a fully self-contained and inexpensive analytical device for on-site analysis of colorimetric data, primarily used in food quality inspection, explosive screening, and biomedical diagnosis.[49] The hand-held device employs a commercial color contact image sensor (CIS) which uses a linear array of CMOS optical detectors to capture sensor images. The small size, low power consumption, and inexpensiveness of CISs make them exceptionally practical for field applications. As a recent example, we compared colorimetric data acquired on the hand-held reader to that from a flatbed scanner and a smartphone camera in the detection of a biogenic amine, trimethylamine (TMA, the active agent in the genetic disease, trimethylaminuria or "fish malodor" syndrome): all three devices provide accurate quantification for a wide range of TMA concentrations with limits of detection (LODs) of 3, 4, and 6 ppb for the hand-held reader, the flatbed, and the smartphone, respectively.[50] Color calibration is easily done using standard methods, as described in the original articles.[27,49,50]

4. STATISTICAL ANALYSIS AND MODELING

In general, statistical or chemometric analysis can be divided into two distinct families: clustering and classification.[51] Clustering methods seek to describe a data set in terms of groups of related targets. Classification methods, on the other hand, attempt to predict information about an unknown sample from previously acquired data.

4.1. Clustering Methods

Descriptive clustering methods, including principal component analysis (PCA) and hierarchical cluster analysis (HCA) are unsupervised (i.e., without a pre-existing library) and show clustering of data, but do not provide predictive classification without additional criteria.

PCA is a dimension-reduction technique that reorthogonalizes data using linear combinations of the initial dimensions to maximize data variance in the fewest possible dimensions.[52] PCA is not useful for data that intrinsically have high dimensionality (e.g., requires more than ~3 dimensions to caption >95% of total variance). For high dimensional data, HCA is the strongly preferred clustering technique and groups data in a multidimensional space using a distance metric (e.g., Euclidean distance) and a clustering criterion (typically, minimization of total in-cluster variance, Ward's method). HCA is commonly employed, for example, to form the dendrograms used for genome comparisons.[51]

4.2. Classification Methods

Classification methods are "supervised", i.e., typically employ predetermined data (a training set or library) to classify unknown samples using linear or other classifiers. Common methods that can maximize the discriminatory ability include hypothetical methods (e.g., linear discriminant analysis (LDA)) or empirical predictive methods (e.g., support vector machines (SVMs)). The classification strategy for LDA is essentially the same as that for PCA: establishing a decision threshold that best separates data sets along a particular vector.[53] SVM is an optimization-based algorithm that determines a well-defined decision boundary to best separates pairwise data.[54] SVM has several advantages over LDA in that it literally addresses two statistical challenges: (i) SVM can function with small sample populations; (ii) SVM works extremely well with highly dimensional data because it requires no covariance information (so avoiding the problem of homoscedasticity encountered by other discriminant methods with sparse data).

5. APPLICATIONS OF COLORIMETRIC SENSOR ARRAYS

5.1. Applications to Single Analytes

5.1.1. Toxic Industrial Chemicals. The chemical workplace has no equivalent of the physicists' radiation badge. Toxic industrial chemicals (TICs) pose serious health risks during workplace handling. Traditional methods for the detection of gas-phase hazardous chemicals mainly include gas chromatography/mass spectrometry, ion mobility spectrometry, and electronic noses. Most of those techniques suffer from limited portability, complicated instrumental operation, long analysis times, poor sensitivity, or poor selectivity. Colorimetric sensor arrays are exceptionally able to incorporate a diverse set of chemically responsive indicators for gas analysis. Our earlier work has demonstrated the success of nanoporous sol–gel or plasticized pigments as chemoresponsive optical sensors in the detection and identification of TICs[1,24] and volatile organic chemicals (VOCs).[26,27,55] For example, we demonstrated excellent discrimination among 20 representative high-hazard TICs at concentrations that are immediately dangerous to life or health (IDLH) within 2 min of exposure (Figure 5a); HCA dendrogram gave accurate clustering results out of 147 trials without misclassification (Figure 5b); similar results occur at the much lower permissible exposure limits (PEL).

LODs for TICs are generally below 5% of their PELs and all well below 100 ppb. Formaldehyde and carbon monoxide were a bit more problematic but have been resolved recently by development of aldehyde- and CO/ethylene-sensitive sensors that can detect as low as ~50 ppb for HCHO[56,57] and ~400 ppb

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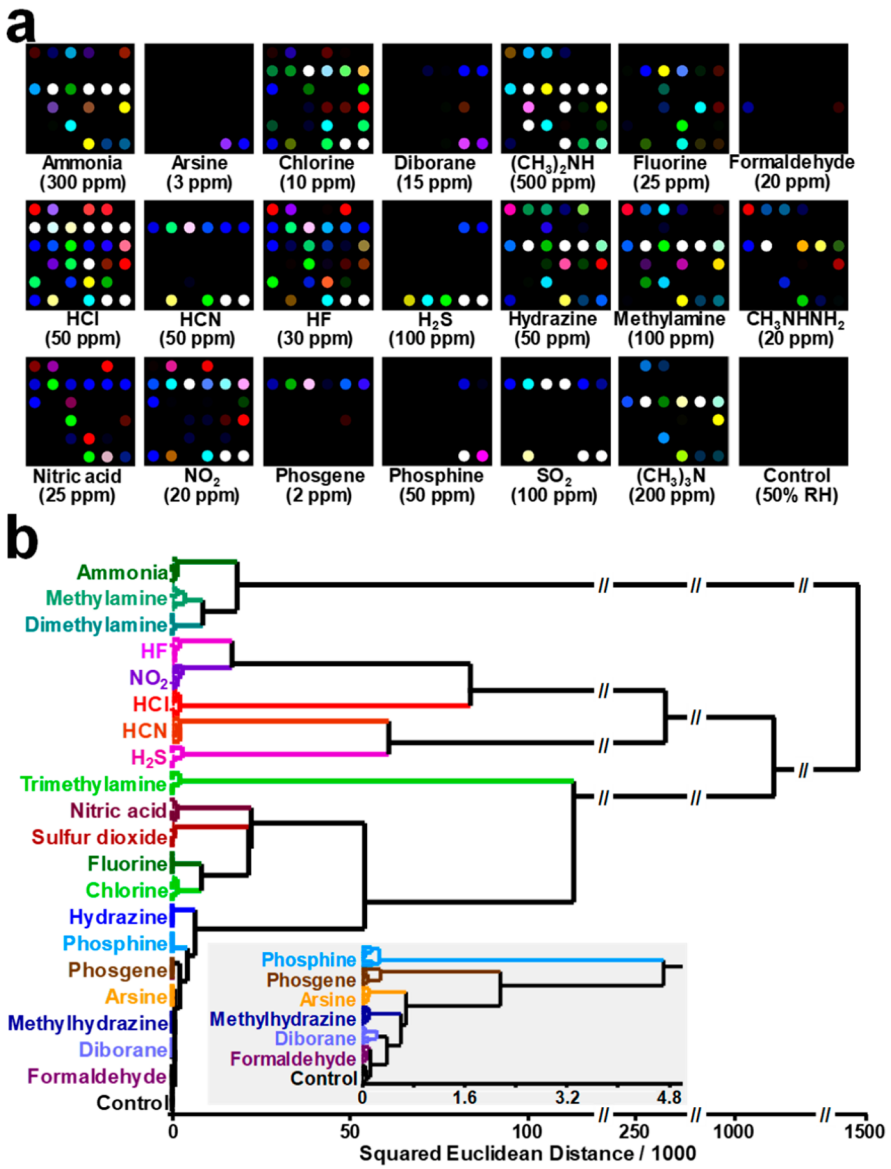

Figure 5. Measurement of 20 highly hazardous TICs using a 6 × 6 colorimetric sensor array. (a) Color difference maps of 20 TICs at their IDLH. (b) HCA of 20 TICs at the IDLH. Adapted with permission from ref 24. Copyright 2010 ACS.

for CO, respectively.[58] The other important index that defines the sensor's discriminatory capability, limits of recognition (LOR), were determined on a subset of TICs (HCN, SO_2, NO_2, NH_3, and PH_3).[59] Here, the LOR is well below 5% of their PELs. Sensitive detection and discrimination of trace amounts of toxic gases may have potentially valuable implications for epidemiological research. A linearized array (Figure 2) extended this approach for the multiplexed screening of off-gases from solid explosives or liquid fire accelerants.[44,45]

5.1.2. Pollutants for Artwork Monitoring and Protection. The conservation of cultural heritage materials demands proper control of the environment in which they are displayed or stored. Works of art in museums are particularly susceptible to airborne pollutants that may cause irreversible and permanent damage. Cost-effective monitoring of potential airborne pollutants is therefore essential to artwork conservation, especially inside closed display cases, during travel, or on exhibit.[60] Taking advantage of the dosimetric nature and chemical diversity of functionalized Ag nanoparticles, the aforementioned aggregative nanoparticle sensor array has been successfully employed for ultrasensitive detection and identification of reactive pollutants of concern to art conservation.[4] Excellent discrimination results among different types and concentrations of individual pollutants were obtained using standard chemometric analyses.

The sensor array can also readily quantitate the outgasses that produce degradation of paper materials and determine the effects of paper formulation, fabrication process, production age, and storage conditions.[37] We applied the array to the nondestructive analysis of acidic emissions from different printing papers, including acid-free substrates such as copier paper and linen-rag archival paper, as well as more acidic bamboo paper and newsprint. To simulate monitoring artwork in a closed microenvironment, the sensor array was placed in an ordinary Ziploc bag with a few sheets of paper (Figure 6a). The array responses after 12 h of gas exposure show distinctive patterns for each type of paper that cluster without error (Figure 6b and c); the clustering is largely dependent on the acidic volatiles emitted. This new cumulative sensor array should prove of real value in the preservation of potentially acidic media, such

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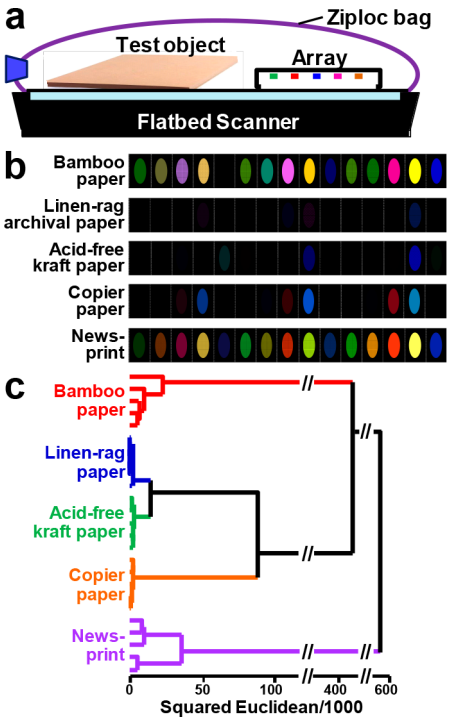

Figure 6. Sensor array detection of acidic volatiles from paper materials. (a) Experimental setup for imaging of the AgNP sensor array during exposure to gas pollutants in a passive sampling environment with an ordinary flatbed scanner. (b) Color difference profiles of volatiles emitted from five different paper materials. (c) HCA dendrogram from quintuplicate trials each for five types of commercial paper. Adapted with permission from ref 37. Copyright 2020 ACS.

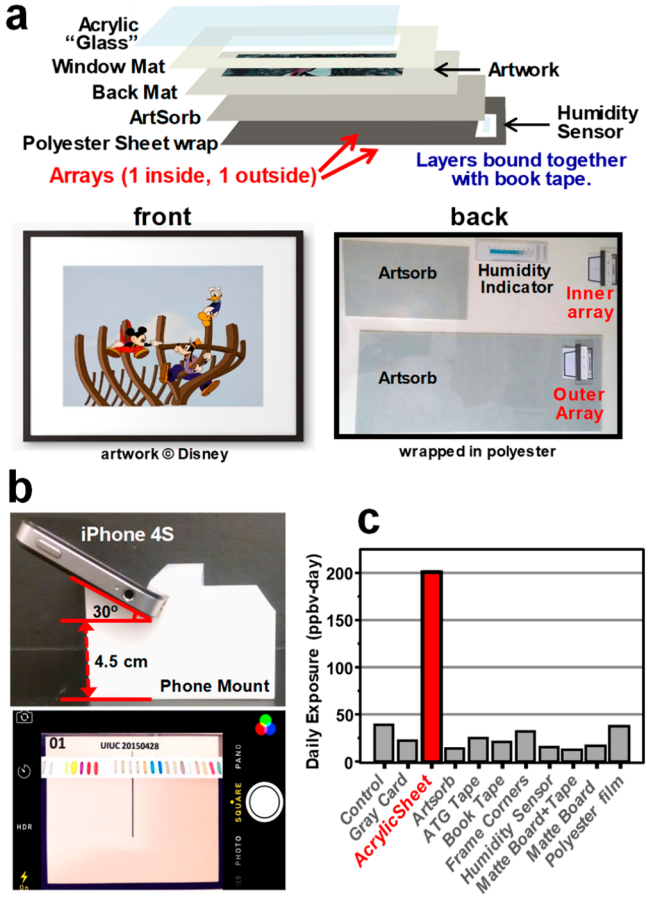

Figure 7. Colorimetric sensor arrays for field monitoring of pollutants inside artwork microenvironments during exhibition. (a) Passe-partout framing used by the Walt Disney Animation Research Library. Artsorb sheets act as a humidistat. Two sensor arrays were mounted to the back of the artwork for pollutant monitoring: one inside the sealed frame and one outside. (b) Smartphone imaging platform used in the field and the sensor array. (c) Time-weighted average (TWA) concentration of sulfide emission observed by the sensor array from each component in the passe-partout packaging. Adapted with permission from ref 60. Copyright 2018 Taylor & Francis.

as nitrocellulose (e.g., pre-1950s cinema films) or paper-containing cultural heritage materials (e.g., antiquarian books, newspapers, or manuscripts).

In a successful transition from laboratory to field trials, we have also monitored pollutant exposure of artwork from the Walt Disney Animation Research Library during the first Disney exhibition in China, titled "Drawn from Life: the Art of Disney Animation Studios", using a smartphone imaging platform.[60] The exhibition featured original animation drawings, story sketches, layouts, and concept art spanning the 90 years of the Disney Animation Studio's history. The sensor array (Figure 7a) integrates several dosimetric redox and pH dyes with dramatically improved sensitivities compared to commercial Dräger tubes. Sensor arrays were deployed both inside and outside of the sealed passe-partout artwork frames on exhibition and inside shipping crates during transport (Figure 7b). The pattern analysis provided quantitative information on the contents of oxidant, aldehyde, and sulfide pollutants. The results clearly demonstrate that the acrylic sheet was a surprisingly significant emitter of off-gassing of sulfides (Figure 7c) and revealed substantial exposure to O_3 and NO_x during shipping. The study also demonstrated that Artsorb sheets (a common humidstat) were also effective in protecting the internal space within the sealed frame from outside pollution.

5.2. Applications to Complex Mixtures

5.2.1. Foods and Beverages. The discrimination among highly similar mixtures often remains problematic even using the most sophisticated analytical methods. The quality control of food and beverages becomes imperative for the regulation of the food market and for protection of consumers' health. Fast and simple analysis of foods or beverages outside of laboratory settings has become an urgent need. Our early studies demonstrated the practical uses of the colorimetric sensor arrays in the discrimination among commercially available brands of coffee,[61] soda,[62] beers,[63] sugars,[64,65] and sweeteners,[66] both in gas and liquid phase analytes.[55]

As recent examples, the linearized colorimetric sensor arrays have been successfully applied to quality assurance of alcoholic beverages[3] and meat products.[67] For the discrimination among liquors, we used our well-established preoxidation technique[68] to convert relatively inert alcohols into more reactive aldehydes, ketones, and other partially oxidized products; the detection of headspace volatiles of liquors was performed using the hand-held gas analyzer (Figure 8a). This sensor array gives distinctive HCA grouping results based on 2 min vapor exposure to each of the 14 liquors and 5 mock controls (i.e., ethanol solutions at equivalent concentrations), as seen in Figure 8b. Real liquors with complicated chemical compositions give more intricate response patterns than aqueous ethanol controls, which provide an effective method for the differentiation between authentic

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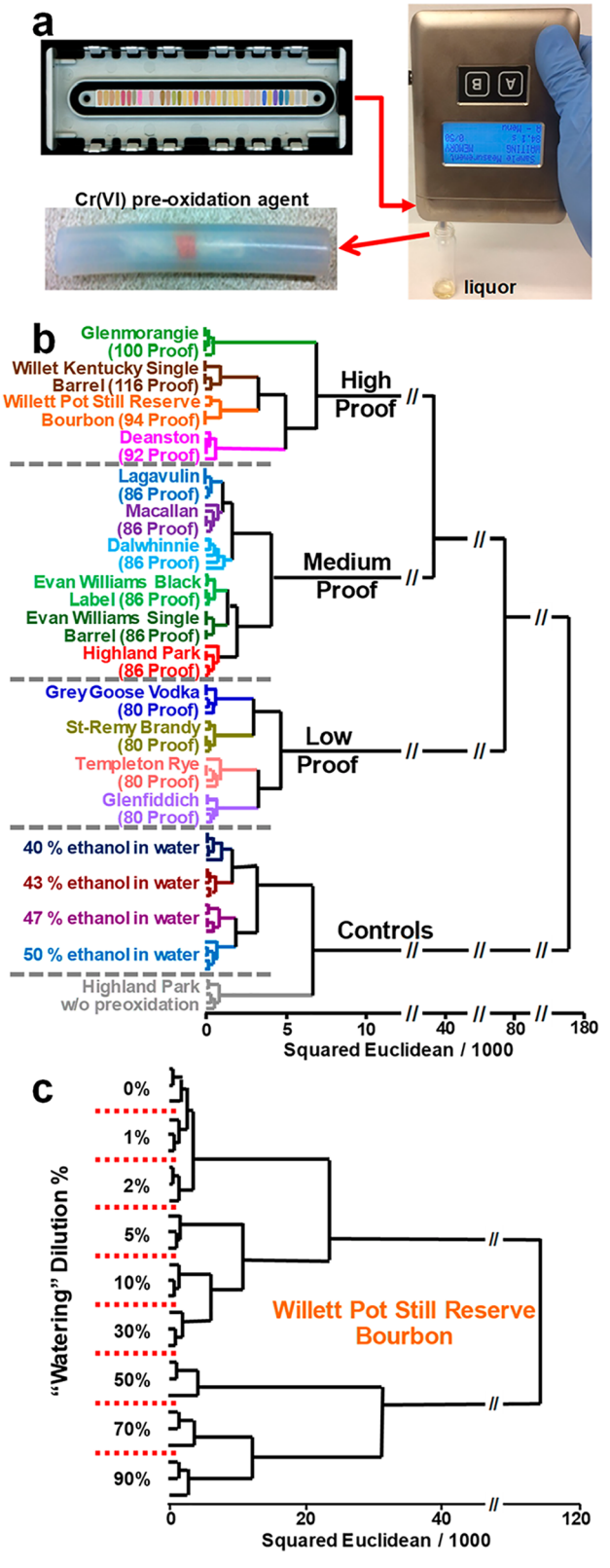

Figure 8. Optoelectronic nose for the discrimination of liquors. (a) Sensing platform composed of a linearized sensor array, a hand-held gas analyzer with a color contact image scanner, and a disposable preoxidation tube that partially oxidized liquor vapors. (b) HCA dendrogram of 14 liquor samples, 4 ethanol controls, and a control from 1 whisky without preoxidation. (c) HCA dendrogram of a single bourbon at different "watering" dilutions. Adapted with permission from ref 3. Copyright 2018 ACS.

and counterfeited liquors. In addition, adulteration by as little as 1% watering was identifiable (Figure 8c).

The optoelectronic nose was also used to detect the freshness of meat products.[67] The introduction of metal ion chromogens into the sensor array greatly improved sensitivity toward representative sulfides and amines, with detection limits at low ppb levels. Sensing outputs from amines emitted in the first 12 h of spoilage and sulfides subsequently produced after 24 h are captured by the sensor array. This enables accurate discrimination among headspace samples of common meat products as a function of storage temperature and duration (Figure 9a). PCA results give separable clustering of the data with three distinctive groups, labeled as "fresher", "less fresh", and "spoiled", respectively (Figure 9b).

5.2.2. Bacteria and Fungi. Arguably, the reason we have olfaction (and why the nose is located just above the mouth!) is to keep us away from high concentrations of microorganisms. Bacteria and fungi stink! They produce a complex mixture of volatile organic compounds produced from their own metabolism to which the olfactory system is highly responsive. As a result, an experienced microbiologist can readily identify various types of microorganisms by smell. Clinical applications of conventional electronic noses, however, have been restricted by their low dimensionality and achieved only modest success in bacterial discrimination.

Our colorimetric sensor arrays have proven to be a useful tool in the identification of microbial species with special relevance to rapid diagnosis of blood sepsis. Our early studies demonstrated the use of the 6 × 6 sensor array to identify strains of human pathogenic bacteria grown on standard agar by discriminating among the complex mixture of VOCs produced from different bacterial strains.[2] By monitoring bacterial growth during 10 h of incubation, 10 strains of bacteria and their antibiotic-resistant strains were distinguishable based on the metabolic profiles of emitted volatiles (Figure 10). PCA, HCA, and leave-one-out LDA demonstrated 98.8% accuracy of data classification out of 164 trials. This work was extended for sepsis diagnosis to 15 pathogenic species and 1900 trials with 99.4% specificity in 3 h culturing.[69,70] We also found that a similar array provided unique composite responses to metabolic volatiles of 12 human pathogenic fungal strains in as few as 3 h of inoculation with a classification accuracy of 94% using the standard jackknifed LDA out of 155 cases.[71] For both bacteria and fungi, sensitivity to added antibiotics was also easily monitored during growth on cultures, making this a viable approach to antibiotic susceptibility testing.[69,70]

5.2.3. Biomedical Analysis and Disease Biomarkers. Breath analysis for disease diagnosis has a long history of research[72,73] and is beginning to emerge as an effective diagnostic approach. Limitations in traditional analytical devices for breath test have restricted their use in clinical and point-of-care settings. Array-based optical sensors have been evaluated for breath analysis, especially for diagnosis of respiratory diseases, such as lung cancer. Mazzone et al. used our colorimetric sensor array for exhaled breath screening of over 200 study subjects, which revealed that lung cancer patients could be well distinguished from control subjects through the adjustment of clinical predictors.[74] Similar results were found for early identification of bacterial infections in comatose patients[75] and tuberculosis from VOCs in urine.[76]

In more recent work, we have explored rapid quantification of trimethylamine *N*-oxide (TMAO), a key metabolite in the diagnosis of human cardiac and kidney diseases. New

https://dx.doi.org/10.1021/acs.accounts.0c00671
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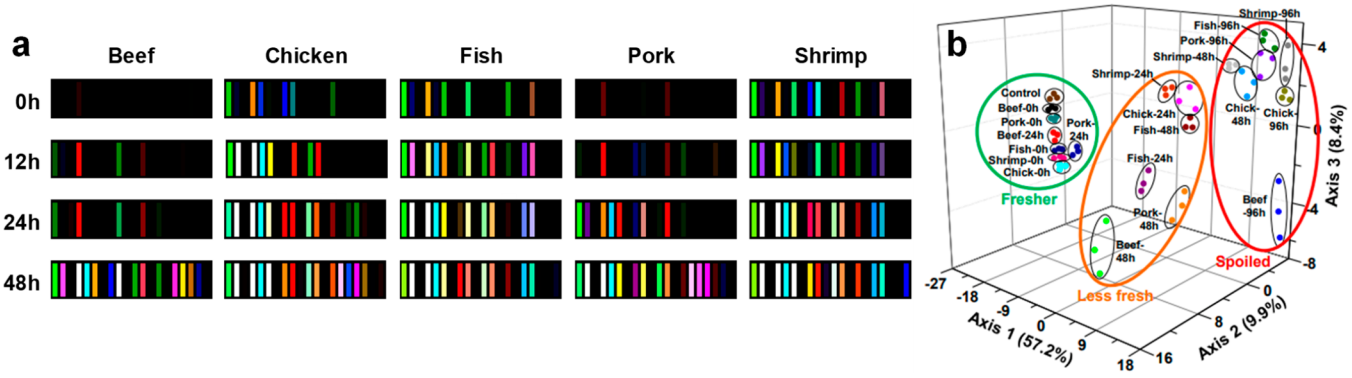

Figure 9. Optoelectronic nose for the discrimination of meat products. (a) Sensor array responses to five meats stored at room temperature. (b) PCA score plot of five meat products stored at room temperature over 96 h; the first 3 dimensions only encompass 75.5% of the total variance, but clean clustering is still observed. Adapted with permission from ref 67. Copyright 2016 ACS.

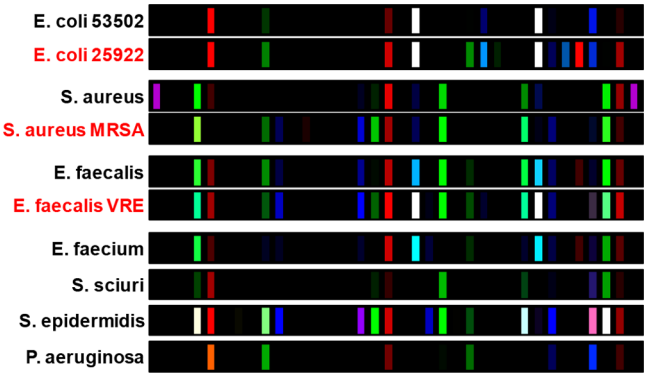

Figure 10. Color difference profiles for 10 different bacterial strains resulting from colorimetric sensor array exposure to Petri dish growing cultures after 6 h of incubation. The red labels indicate antibiotic resistant strains compared to nonresistant strains immediately above each. Adapted with permission from ref 2. Copyright 2011 ACS.

approaches for rapid quantification of elevated TMAO levels in body fluids would be extremely useful for point-of-care diagnoses. Sensors made of porous silica-dye microspheres were prepared for rapid determination of urinary TMAO concentrations.[48] A 13-element colorimetric sensor array showed an enhanced sensor response to trimethylamine vapors generated from the catalytic reduction of TMAO (Figure 11a); the detection limit of urinary TMAO is ~4 μM, which is well below the median concentrations (380 μM) among healthy human subjects. Both HCA and PCA give >99% accuracy in the clustering of all tested concentrations. This colorimetric sensor array could potentially serve as a quick and inexpensive point-of-care tool for the early diagnosis of TMAO-relevant diseases.

6. CONCLUSIONS

The optoelectronic nose, based on pattern recognition of the color changes of colorimetric sensor arrays, has emerged as a versatile approach for the identification of chemically diverse analytes and the discrimination among similar complex mixtures. In this Account, we have discussed a variety of applications of optoelectronic noses, including personal dosimetry of toxic industrial chemicals, detection of explosives or fire accelerants, monitoring pollutants for artwork and cultural heritage preservation, quality control of foods and beverages, rapid identification of bacteria or fungi, and detection of disease biomarkers in breath or urine.

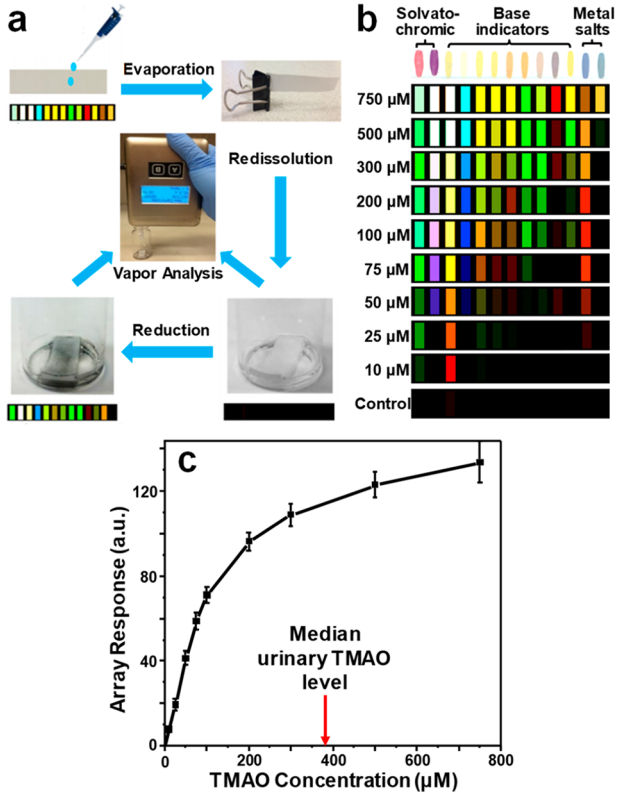

Figure 11. Optoelectronic nose for hand-held analysis of urinary TMAO. (a) Procedures for the removal of volatile amines, reduction of TMAO using Raney Ni/$NaBH_4$, and analysis of newly generated amines in a simulated urine sample; the colored pattern under each vial reflects the overall level of volatile amines as detected. (b) Color difference profiles of the sensor array after 2 min exposure to amine vapors released from the reduction of TMAO at different concentrations. (c) Response curves of the sensor arrays over a wide range of TMAO concentrations. Adapted with permission from ref 48. Copyright 2018 ACS.

The rapid improvements in digital imaging and computational power suggest that future optoelectronic noses will take advantage of ordinary cell phones linked to Bluetooth readers the size of a pen holding a disposable sensor array. The development of portable, high-accuracy instrumentation using standard imaging devices with the capability of onboard, real-time analysis has had substantial progress and increasingly meets the expectations for real-world use.

https://dx.doi.org/10.1021/acs.accounts.0c00671
Acc. Chem. Res. 2021, 54, 950−960

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Notes

The authors declare the following competing financial interest(s): Z.L. declares no competing financial interests. K.S.S. is a founding shareholder of iSense LLC and Specific Diagnostics, Inc.

Biographies

Zheng Li received his B.S. in Chemistry from Nanjing University in 2012 and his Ph.D. in Chemistry from the University of Illinois at Urbana−Champaign in 2017 under the guidance of Prof. Kenneth. S. Suslick. He was a postdoctoral research associate with Prof. Qingshan Wei at the North Carolina State University, 2018−2019. He is currently an Assistant Professor at the Institute for Advanced Study, Shenzhen University. His research interest includes the development of new chromogenic or fluorometric materials and the design of portable sensing devices for a wide range of applications in health diagnosis, security screening, environmental monitoring, and agricultural and food inspection.

Kenneth S. Suslick is the Marvin T. Schmidt Research Professor of Chemistry at UIUC. Professor Suslick received his B.S. from Caltech in 1974, his Ph.D. from Stanford in 1978, and came to Illinois immediately thereafter. Among his awards are the Centenary Prize and the Sir George Stokes Medal of the RSC, the MRS Medal, the ACS Hildebrand Award, Nobel Laureate Signature and Cope Scholar Awards, the Helmholtz-Rayleigh Silver Medal of the ASA, and the Chemical Pioneer Award of the AIC. He is a Fellow of the National Academy of Inventors, ACS, APA, ASA, MRS, and AAAS.

ACKNOWLEDGMENTS

Z.L. acknowledges financial support from the National Natural Science Foundation of China (No. 22076125), Guangdong Joint Fund of Fundamental and Applied Research (No. 2019A1515110242), and Guangdong University Young Talents Project (No. 2019KQNCX127). K.S.S. acknowledges past funding in this research area by NIH, DHS, NSF, and DoD, and by the Proctor & Gamble Foundation.

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