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Prospects and Challenges of Volatile Organic Compound Sensors in Human Healthcare

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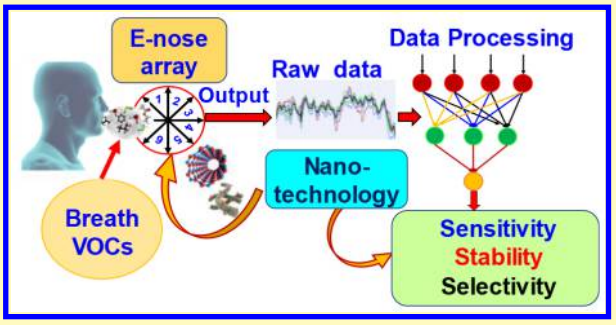
ABSTRACT: The chemical signatures of volatile organic compounds (VOCs) in humans can be utilized for point-of-care (POC) diagnosis. Apart from toxic exposure studies, VOCs generated in humans can provide insights into one's healthy and diseased metabolic states, acting as a biomarker for identifying numerous diseases noninvasively. VOC sensors and the technology of e-nose have received significant attention for continuous and selective monitoring of various physiological and pathophysiological conditions of an individual. Noninvasive detection of VOCs is achieved from biomatrices of breath, sweat and saliva. Among these, detection from sweat and saliva can be continuous in real-time. The sensing approaches include optical, chemiresistive and electrochemical techniques. This article provides an overview of such techniques. These, however, have limitations of reliability, precision, selectivity, and stability in continuous monitoring. Such limitations are due to lack of sensor stability and complexity of samples in a multivariate environment, which can lead to false readings. To overcome selectivity barriers, sensor arrays enabling multimodal sensing, have been used with pattern recognition techniques. Stability and precision issues have been addressed through advancements in nanotechnology. The use of various forms of nanomaterial not only enhance sensing performance, but also plays a major role in detection on a miniaturized scale. The rapid growth in medical Internet of Things (IoT) and artificial intelligence paves a pathway for improvements in human theranostics.



KEYWORDS: *volatile organic compounds, biofluids, sensors, real-time, sensitivity, selectivity, stability*

Detection of volatile organic compounds (VOCs) as biomarkers of different diseases and disorders allows diagnosis and therapy of several ailments in real-time, noninvasively.[1] The levels of VOCs provide an understanding of one's physiological and pathophysiological condition. These VOCs are specific to certain diseases and can be employed as olfactory biomarkers of metabolic, genetic, infectious, cancerous, and other kinds of diseases.[2] Through their easy accessibility in different clinical biomatrices, reliable and continuous monitoring of such conditions is made possible for management of wellness in real-time. Noninvasive sensing techniques promote diagnostic management as and when necessary. Wearable sensors and sensor arrays (e-noses) play a role in continuous monitoring of specific diseases, such as lung cancers, renal diseases, and diabetes.[3−6]

According to International Union of Pure and Applied Chemistry (IUPAC), "biosensors are considered as devices that transform biochemical information into an analytically useful signal."[7] For timely evaluation of one's concerned health condition, the biosensors need[4,5] (i) accurate measurement, (ii) rapid assessment, and (iii) selective detection. These properties of the sensor enable a physician to accurately diagnose the specific disease and initiate required therapy to prevent further aggravation of the disease. The phenotypic characteristics of their excretion can be analyzed through the observation of their real-time VOC data.[6] Besides biosensing techniques, various analytical methods are used to accurately measure VOCs in breath. However, they are not only expensive but also lack portability.[8−12]

Biosensing techniques such as chemiresistive, optical, piezoelectric, electrochemical, and surface acoustic wave (SAW) sensors have prominent prospects in VOC detection on a wearable platform.[13−17] These sensors have been miniaturized by advancements in micromachining and nanotechnology.[18] Incorporation of nanomaterial is known to influence its sensing performance and assists in multisensing arrays platform.[18,19] The use and combination of different kinds of nanomaterial is therefore gaining interest in design of clinical and diagnostic tools, due to its advantages of higher surface-to-volume ratios. Their specific forms provide faster response and recovery times, in addition to support specific detection through suitable alterations of their physical and chemical properties. Assisting in very-large-scale integration

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manufacturing and miniaturization to enable portability, they allow integration in point-of-care devices.[20]

Selective detection is yet to be overcome in existing VOC sensing approaches. This is due to the complex composition of the sampling matrices. Different intrinsic (e.g., hysteresis, fouling effect) and extrinsic ambient parameters (e.g., humidity, temperature) can also interfere with precise detection in a multivariate environment, coupled with signal degradation over time.[21−23] Detection using multiple sensors on the same platform improves the response through elimination of mentioned interefrents.[23] More detailed information on one's physiological condition can be obtained through integration of e-noses on a multimodal sensing (e.g., skin temperature, gyroscope, etc.) platform.[24] Such sensing modalities provide a better understanding of one's physiological condition, enabling accurate detection in real-time.[25]

The use of sensor arrays (e-noses) and techniques entailing different pattern recognition (unsupervised) and classification (supervised) approaches targets specific VOC detection from a multivariate environment.[26] Different pattern recognition and machine learning approaches assist in reducing the redundancy of acquired data, aiming toward improved selectivity, specificity, and stability.[27−29] Once data is collected by multisensors array or e-noses, it goes through transformation, filtering process, and is fed to a genetic algorithm for searching. Further, a predefined prediction model and regression method promote precise calibration in multivariate environment.[30] Such methods provide a pattern in diagnosis, through cross-validation in different population sectors.

With growing interest in VOC detection, this article delineates: (i) a comprehensive analysis of different biofluids to identify possible VOCs as biomarkers and potential biofluids for VOC sensing in real-time, (ii) a detailed overview of different sensing techniques to detect numerous VOCs from the biofluids, and (iii) the prospects and challenges of different VOC sensors and their possible solutions for healthcare.

BIOFLUIDS AS THE SOURCE OF VOCs

Recent research suggests that 1849 VOCs have been found in different biofluids.[31] Such biofluids include blood, interstitial fluids, breath, sweat, saliva, urine, serum, breast milk, tears, and feces (Figure 1a). Figure 1b shows that breath and skin are the potential sources of VOCs (54% of total amount), with 15%, 14%, 11%, and 6% of them being present in feces, saliva, urine, and blood, respectively.[32] These sources are feasible for either invasive or noninvasive detection of VOCs for diagnosis of diseases.

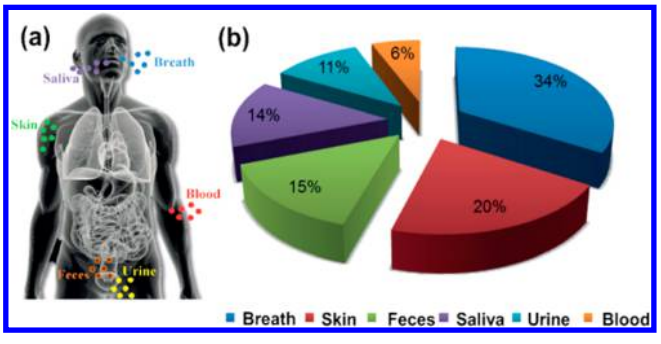

Figure 1. (a) Different biofluids of VOCs in the human body,[32] (b) VOC percentages in different biofluids following the data of healthy human.[32] Reprinted with permission from ref 32. Copyright 2015 Wiley-VCH Verlag GmbH &Co. KGaA, Weinheim.

SOURCES FOR INVASIVE DETECTION

Blood and Plasma. Blood has been considered as a reliable matrix to characterize the physiological condition of an individual. There are 154 different VOCs that have been discovered in blood yet.[33] These VOCs are the biomarkers of many diseases and reflect the internal status of the human body pertaining to nutritional, metabolic, and immune conditions.[32] Blood contains different volatile compounds: typically, acetonitrile, ammonia, ethers, alkanes, alcohols, benzyl, and phenyl hydrocarbons.[33] The metabolic and immune status of any human can be reliably deliberated from the blood sample analysis of infrequent amounts of specific VOCs. For example, benzene and toluene levels in blood increase due to smoking, while trihalomethane levels in blood are high in swimmers with elevated levels of chloroform.[34,35] Levels above the normal for any of these exogenous compounds can be detrimental to human health. High doses of chloroform could lead to liver toxicity, providing a pathway for other fatal diseases with reduced red blood cells, causing anemia and DNA breakage. Horvath et al. suggests specific aroma(s) in blood can be a suitable tool for screening different kinds of cancer or internal disorders, like ovarian carcinoma, lung cancer, and hepatic encephalopathy.[36] Plasma derived endogenous VOCs in blood have attracted researchers for early cancer detection (e.g., gynecological, lung, etc.). Selyanchyn et al. introduced an analytical method to assess VOCs in blood for cancer detection.[37] In their work, VOCs of blood plasma have been differentiated in between of carcinogenic and benign controls precisely. Although blood tests are more consistent than detection from other biofluids, obtaining blood samples is arduous, inefficient, invasive, and inapplicable for instantaneous POC applications.

Interstitial Fluids (ISFs). Different ISFs such as cerebrospinal fluid (CSF), peritoneal fluid, pleural fluid, biliary fluid, synovial fluid (SF), or pericardial fluid (PCF) are also analyzed to diagnose different diseases. The presence and analyses of VOCs in such biofluids are limited in discussion of literature. Liu et al. explored 76 different pleural samples and found three major groups: ketones, alcohols, and benzene derivatives dominating for cancer malignancy. Among 76 VOCs, 9 of them including dichloromethane, ethyl acetate, *n*-heptane, ethyl-benzene, xylene, cyclohexanol, cyclohexanone, 2-ethyl-1-hexanol, and tetramethylbenzene are potential compounds for screening lung cancer to differentiate malignant from benign pleural effusions. Conditions such as tuberculosis, pneumonia, congestive heart failure, and cirrhosis are the cause of benign effusions, where 30% of malignant effusion is associated with lung cancer.[38] VOC analysis of biliary fluid can also distinguish malignant cholangiocarcinoma from benign biliary strictures. It can be used as a potential biomarker for pancreatic cancer by classifying the concentration spectra of tetramethyl acetate, acetone, acetaldehyde, benzene, carbon disulfide, and pentane.[39] The presence of inflammation and oxidative stress modulate the release of VOCs from SF which cause osteoarthritis and rheumatoid arthritis. Tominaga et al. conducted toxicological analysis for serial forensic autopsy cases and compared PCF with peripheral blood to reassess the post-mortem distribution of ethanol and to examine the dispersal of other VOCs.[40] However, the invasive nature of the

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detection mechanism from ISFs is always laborious, expensive, and inefficient for real-time detection.

SOURCES FOR NONINVASIVE DETECTION

Urinary Biofluid. Urine tests are an established method to detect several diseases noninvasively. The aqueous urinary matrix contains a small percentage of VOCs.[41] Renal activities control the supply of endogenous and exogenous VOCs in urine. Endogenous VOCs comprise ketones, alcohols, heterocyclic compounds, different hydrocarbons, amines, aldehydes, and organic acids.[41] Ketones are the most common VOCs that can be produced through breakdown of fatty acid due to oxidation. Ketone levels can rise from normal due to starvation (fasting ketosis, FK), consumption of low carb-high fat diet (nutritional ketosis, NK) and alcohol; and prolong exercise. The raising state of NK provides energy to the brain to epileptic patients.[42] The elevated level of ketones in urine is also a biomarker of hyperglycemia or diabetic ketoacidosis (DKA). Inadequate ketogenesis causes hypoglycemia whereas excessive presence of ketones leads to ketoacidosis. However, DKA is a severe case with ketone levels increasing to more than twice, as compared to other states of ketosis.[43] As ketone levels depend on multiple physiological parameters (e.g., energy stability, diet composition, physical activities and diseases), accurate diagnosis of one's ketone profile is critical to identify actual physiological condition.[42] Like ketones, other VOCs in urine are also possible biomarkers of many diseases and can provide a certain profile for the VOC depending on dehydration, diet, liquid and drug intake. Elevated levels of acetonitrile in urine confirms whether someone is a smoker or not.[44] Urinary metabolomics studies have been employed to different cancer studies, such as breast, colorectal, esophageal, pancreatic ductal adenocarcinoma, prostate, and liver cancers.[45] Analyzing four different VOCs (2,6-dimethyl-7-octen-2-ol, pentanal, 3-octanone, and 2-octanone), Khalid et al. demonstrated the detection of prostate cancer.[46] Matsumura et al. demonstrated ex-vivo analysis of urinary VOCs as biomarkers for lung cancer.[47] Arasaradnam et al. differentiated celiac disease from irritable bowel syndrome (IBS) and Banday et al. demonstrated tuberculosis diagnosis by using gas chromatography−mass spectrometry (GC-MS).[48,49] Testing of urine in a noninvasive form of detection are reliable though sample collections, handling, preservation, and analysis are cumbersome complications. Hence, diagnosis of VOC biomarkers is technically complex from the urinary sample and this biofluid is not suitable for continuous monitoring.

Saliva. Saliva is known to contain 360 different kinds of exogenous and endogenous VOCs.[32] Like breath, different food debris, drugs, xenobiotics and environmental pollutants can affect various exogenous compounds in detecting VOCs from saliva. Active and passive diffusion of VOCs from blood and ultrafiltration techniques are among the most common approaches used for VOC detection in saliva.[50] 300 different bacterial species have been explored as sources of VOCs in saliva. Major VOCs in saliva include acetic acid, ester, acetonitrile, mercaptan, methyl sulfide, different alkanes, diene, different aromatic compounds (e.g., benzene, toluene, xylene), polycyclic hydrocarbons (carane, copaene, etc.), alcohols (ethanol, propanol, butanol, etc.), and aldehydes (acetaldehyde, propanal, etc.).[31,33] Recent research suggests salivary fluid can be a potential biofluid for noninvasive, continuous, and instantaneous monitoring of different diseases. Several research groups investigated the integration of electrochemical sensors into mouth-guards for monitoring biomarkers.[51] In contrast with other biofluids, the salivary biofluid provides a significant amount of fluid for a greater functioning space for the placement of the sensing unit. With an abundance of VOCs in saliva, this is one of the promising biofluids for continuous and real-time monitoring of different diseases.[51]

Skin Perspiration and Sweat. Human skin is the largest organ in human body and it offers long-lasting emanation of VOCs. Costello et al. mentioned 532 different VOCs are derived from skin secretion through diffusion of sweat.[33] Main VOCs from the skin of a healthy individual include ammonia, carboxylic acid, alcohols, hydrocarbons, ketenes, terrenes, aldehydes, esters, heterocyclic compounds, and volatile sulfur compounds.[52] The profiles of these VOCs differ due to heterogeneous distribution of sweat glands beneath the skin and the metabolism of symbiotic microbiota on the skin surface. The existing clusters of bacteria on the skin contribute to the odor of individuals.[53] Internal excretion of VOCs through skin, however, depends on secretion from its three major glands: i. apocrine gland, ii. eccrine gland and iii. sebaceous gland. Osmosis plays a major role in the transmission of VOCs through these glands and secretion through sweat. Secretion of VOCs can fluctuate with time and change with physiological conditions. This emission pattern, as discussed, can vary with diet, xenobiotics, drugs, psychological stress, wounds, dehydration, shock, body temperature, age, menstrual cycle, and ambient parameters (e.g., temperature, relative humidity, and pressure).[54] Boman and Maibach have verified VOC transmission through skin with diffusion studies on different VOCs using Franz cell diffusion method.[55] Aside from endogenous VOCs, different xenobiotics can be emitted through skin after their metabolism in body. For example, 1% of overall consumption of alcohol is excreted in a diffusive manner from the exocrine sweat gland of skin following specific partition ratio (Henry's law).[22] Human sweat and skin perspiration are potential sources for noninvasive medical diagnostics with their simpler sample collection process. These also offer unique facilities of safety and continuous and real-time monitoring.

Breath. In 1971, Linus Pauling confirmed that human breath is a complex volatile mixture of more than 250 different VOCs. Considering endogenous and exogenous VOCs, 874 types of VOCs have been found in exhaled breath.[31] Major VOCs of human breath in healthy individuals include acetone (1.2−900 ppb), ethanol (13−1,000 ppb), methanol (160−2,000 ppb), isoprene (12−580 ppb), ammonia, and minor components including pentane and higher chains of alcohols, aldehydes, and ketones.[56] Internal conditions, environmental exposure, diet, and lifestyle (e.g., alcohol consumption) of individuals influence the concentration ratio of VOCs in their breath called "exposomes". Thus, the aroma of "exposomes" can vary from person to person. For example, smoking cigarettes leads to high concentrations of acetonitrile and furans. Likewise, elevated levels of isoprene are considered an indication of exertion and it enhances alveolar ventilation and causes isoprene level to raise 3−4-fold.[33] Similarly, an acetonic smell might be associated with hysterical diabetes; or a pungent odor might indicate liver disease.[57,58] Similarly, elevated levels of ethane and pentane are symptoms of different chronic lung diseases, such as malignant pleural mesothelioma (MPM), cystic fibrosis, asthma, or chronic obstructive pulmonary disease (COPD).[59] Mazzatenta et al.

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described that the average amount of VOCs decreases in an Alzheimer patient. Comparing with healthy controls, it appeared the disease altered the brain metabolism due to the death of neurons and their pathological state.[60] Detection of specific VOC from breath is a challenge as there is always a possibility to obtain false readings with the presence of exogenous compounds.

Other Sources. Feces, tears, and breast milk are other common sources of VOCs. Fecal samples currently constitute about 480 VOCs.[32] In feces, diverse exogenous elements are present due to consumption of medication and nutrients which generate extrinsic volatile and nonvolatile metabolites. Bacterial fermentation and microbiota are responsible for the specific odor of feces, which results from colonic fermentation of amino acids. Along with these, some putrefactive chemical compounds are also present, such as aliphatic amines, ammonia, branched-chain fatty acids, short chain fatty acids, derivatives of phenol or indole, and volatile sulfur containing compounds.[32] Different aldehydes, such as acetaldehyde have been produced from dietary and microbial metabolism which have found relevance with colon and pancreatic cancer.[61] Fecal VOCs, like those arising from *Vibrio cholerae*, can be potential biomarkers of different gastrointestinal diseases. Similarly, Gulber mentioned recently the existence and detection mechanism of pheromone (a cocktail of VOCs) in ocular matrix as a biomarker of emotion and mood.[62] Pellazari et al. studied the detection of VOC from maternal milk to reveal that 156 "purgeable" compounds can be studied form it as pollutants that would affect a nursing infant.[63] GC-MS studies on its analyses have shown that, among the different VOCs present in human milk, 45 are odor-active constituents, comprising groups of monocyclic aromatic amines,[64] phthalate esters,[65] and benzene, and alkylbenzenes.[66]

METABOLISM AND KINETICS OF VOCs

The mechanism of metabolism and kinetics of VOCs in the human body is an intricate process. The profiles of different VOCs vary based on several internal and external factors. The advancement of analytical tools allows for the total number and classification of VOCs in different biofluids to be better identified in the present days.[31] These VOCs are classified into two groups: endogenous and exogenous. The generation of exogenous VOC production follows five steps:[67] liberation, absorption, distribution, metabolism, and excretion. Contrarily, metabolism and excretion are the key mechanisms for the generation of endogenous VOCs. In both the cases, however, metabolism is a vital step in production through synthesis (anabolism) or breaking down of compounds (catabolism).

Metabolism of VOCs. Endogenous VOCs are produced due to regular and abnormal metabolic processes occurring in the body. The most common reason for VOC generation is the destruction of cells from direct or indirect oxidative stress and inflammation of the human body.[32] Molecular oxygen is required to protect cellular metabolism; therefore, equilibrium of oxygen is maintained within the human body through homeostasis. As a process of energy generation in mitochondria, 1−5% of oxygen molecules are reduced to water molecules by the cytochrome through catalyzed electron transport chain reactions. This intercell energy conversion process relies on any of the following four processes:[68] (i) reactive oxygen species (ROS), (ii) hydrogen peroxide formation, (iii) generation of hydroxyl radical, and (iv) superoxide formation. Among them, ROS have been identified as the chief contributors to many neurological, inflammatory, cardiovascular, and immunological diseases along with progression of aging.[69] The formation and disintegration of ROS in mitochondria trends toward equilibrium and many hydrocarbons have been bound to the oxygen species in the process of mitochondria to cytoplasm conversion. Molecular structures of the cell with proteins, DNA, RNA, and poly saturated fatty acids get affected and disintegrate due to the presence of accumulated ROS.[70] Different hydrocarbons have been generated during this process, and they may further oxidize and produce different kinds of alcohols, aldehydes, and ketones. Different microbials and enzymes are involved in the further metabolic processes, which therefore generates many different VOCs. For example, alcohol is metabolized by alcohol dehydrogenase due to three different kinds of enzymes: aldehyde dehydrogenase (ADH), cytochrome P450 (CYP2E1) and catalase;[71] these convert the ethanol into acetaldehyde and later into nontoxic acetic acid. Likewise, ADH enzymes enhance metabolic activity and produce carboxylic acids through the disintegration of aldehydes. Different VOCs are also generated from dead cells in the human body. 1,3-Di-*tert*-butylbenzene, 2,6-di-*tert*-butyl-1,4-benzoquinone, and *n*-decane were found in dead lung cancer cells due to apoptosis and necrosis.[72]

Exogenous VOCs are mainly absorbed from food and drink which reach to the gastrointestinal tract, metabolized mostly in the liver and kidneys. The liver is the key organ which is actively involved in both catabolism and anabolism of many exogenous VOCs, creating a route to stream blood from the intestine. Thus, VOCs in fecal samples in the gastro-intestinal tract go through a probable transformation in the liver before being distributed to the blood, reaching the lungs and appearing in breath. As mentioned earlier, the liver is the bed for large varieties of enzymes where ADH is actively involved in the oxidation of nonpolar VOCs, converting them into conjugate compounds.[71] Likewise, it contains a large quantity of CYP2E1 and is a mixed function oxidase system, actively involved with the transformation of xenobiotics. Nonpolar hydrocarbons are transformed into polar alcohols/aldehydes which convert to acids via the process.

Kinetics of VOCs. After metabolized in liver, VOCs are distributed through blood. The change in VOC over time in the liver is described by the mass balance equations as follows:[73]

$$V_{\text{liver}}\frac{dC_{\text{liver}}}{dt} = Q(C_{\text{LVM}}\text{-})C_{\text{liver}} + (k_s V_{\text{stomach}} C_{\text{stomach}}) - \frac{V_{\max} C_{\text{liver}}}{k_m + C_{\text{liver}}} \quad (1)$$

$$V_{\text{LBM}}\frac{dC_{\text{LBM}}}{dt} = -Q(C_{\text{LVM}} - C_{\text{liver}}) \quad (2)$$

where $k_s V_{\text{stomach}} C_{\text{stomach}}$ refers to the stomach emptying rate in mol/min. The amount of liquid compound moving out of the liver and into the lean body mass (LBM) is governed by the difference respective to the compound's concentrations (C_{LBM} and C_{liver}) at a rate controlled by the blood flow rate, Q. According to Michaelis−Menten kinetics, the present concentration limited by $V_{\max}$ follows enzymatic reactions represented by the end segment in eq 1.[74] Equation 2 describes the change in its concentration in the LBM based on the concentration of that in the liver at a rate governed by the blood flow rate, Q.

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Apart from the liver, the kidneys and lungs play a significant role to metabolize many VOCs. The mass balance equations (eq 1 and 2) can be similarly applicable for both the kidneys and lungs, considering their own parameters.[73,74] The compound in the bloodstream diffuses through the epidermis and stratum corneum. Blood boundary concentrations are driven by the body VOC concentration from the kinetic phenomenon that sets a concentration gradient through the epidermis and stratum. The total partial pressure is[75]

$$\frac{dP_t}{dt} = D_e\frac{\delta^2 P_e}{dx^2} + D_s\frac{\delta^2 P_s}{dx^2} \quad (3)$$

where $0 \le x < L_e$ and $L_e \le x < L_e + L_s$. For eq 3, D_e and D_s are the molecular diffusivity, L_e and L_s are the thickness of the epidermis and stratum conium, respectively.

The exogenous VOCs can also reach inside the human body through inhalation; and limited extents of them are absorbed through the skin. Inhalation of VOCs occurs through regular absorption process mostly in the alveoli of lungs. The VOC molecules diffuse through the thin capillaries and alveolar type I cells in both directions and reach equilibrium thermodynamically.[76] Partition coefficient of blood and air ($\lambda_{b:a}$) governs this phenomenon and it is one of the major determinants of pulmonary uptake of VOCs. Rapid blood flow in the lungs creates a higher concentration gradient of uptake VOCs, which results in rapid diffusion into blood. As per classical gas exchange theory, the alveolar partial pressure of VOC, normalized to the mixed venous partial pressure, is interrelated to the blood-air partition ratio ($\lambda_{b:a}$) and the ventilation to perfusion ratio (V_A/Q) as follows:[77,78]

$$\frac{P_a}{P_V} = \frac{\lambda_{b:a}}{\lambda_{b:a} + V_A/Q} \quad (4)$$

Farhi's equation represents alveolar concentration (C_a) that is derived as follows from eq 4:[79]

$$\frac{C_a}{C_V} = \frac{1}{\lambda_{b:a} + V_A/Q} \quad (5)$$

Here, C_V is the mixed venous concentration. Respiratory rate and the fraction of the molecules that exist at alveolar tract are also the major factors of this transmission. The higher value of the coefficient ensures greater VOC uptake during inhalation, even in an order of 12-fold of magnitude.[32] Partition coefficient varies with respect to polarity and solubility of VOCs in blood with the range of $10 < \lambda_{b:a} < 100$. Here, the partition coefficient is $\lambda_{b:a} < 10$ for nonpolar VOCs and the highly blood soluble polar VOCs have the partition coefficient as $\lambda_{b:a} \ge 100$. The partition ratio of fat to blood, $\lambda_{f:b}$, is also vital in kinetics of VOCs. These two physiochemical partition coefficients govern the balance concentration of VOCs in breath, blood, and fat. Poulin and Krishnan projected the value of $\lambda_{b:a}$ and $\lambda_{f:b}$ from the known partition ratios of water–air $\lambda_{w:a}$, and octanol–water ($\lambda_{o:w}$) as follows:[70]

$$\lambda_{b:a} = \lambda_{o:w}\lambda_{w:a}(a + 0.3b) + \lambda_{w:a}(c + 0.7b) \quad (6)$$

$$\lambda_{f:a} = \lambda_{o:w}\lambda_{w:a}(A + 0.3B) + \lambda_{w:a}(C + 0.7B) \quad (7)$$

where $a \approx 0.0033$ represents a portion of neutral lipids in blood; $b \approx 0.0024$ represents phospholipids in blood; $c \approx 0.82$ is water in blood; $A \approx 0.798$ is neutral lipids in adipose tissue (fat), $B \approx 0.002$ is phospholipids in adipose tissue, and $C \approx 0.15$ denotes water in adipose tissue. As discussed earlier, these absorbed compounds are distributed to other organs.

DIFFERENT SENSING TECHNIQUES FOR THE DETECTION OF VOCs

Different analytical methods, such as GC-MS, are acclaimed for its precise and specific detection.[80] However, performance on a miniaturization scale has yet to be achieved. Such form factors for optical, chemiresistive, and electrochemical approaches have been achieved through advances in nanotechnology involving micro/nano scale fabrication.[13,14,16] Advancement of synthesis process allowed to be tailored the shape, size, and assembly of different nanomaterials with extensive variation of compositions and crystal structures, such as nanoparticles, nanorod, nanotubes, nanospheres, nanoflakes, nanosheets, hollow spheres, hierarchical nanoarchitectures, and octahedral.[20,81] The large electroactive surface area to volume ratio of these crystals enhances the sensitivity and their well-defined crystal lattice leads to control catalytic reactions for stability of the sensors.[20] The open pores and large voids of various nanostructures enhance response and recovery time of gas sensing.[18] These crystals are typically formed by different carbon allotropes (e.g., graphene, carbon nanotubes) and noble metals (e.g., Au, Ag, etc.) or metal oxides (e.g., SnO_2, ZnO, TiO_2, WO_3, In_2O_3, etc.).[38,82] Among them, ZnO and SnO_2 were widely explored for biosensing for their high quantum yields, high refractive index, wide band gap (~3.37 eV), and high binding.[83,84] The conductivity of these types of sensors can be altered through variation of different parameters (e.g., radius, interparticle distance, dielectric constant of interparticle medium) of nanoparticles.[85] Their sensing performance can be further improved through tailoring their surface area in a metal–organic-framework (MOF).[86] Different potential VOC sensors for real-time detection, their sensing mechanism, limitations and prospects are discussed in the following section.

Optical Sensors. Optical sensing is a potential sensing method for the detection of VOCs in healthcare and wellness management. This detection approach is preferred over other conventional analytical techniques, different spectroscopic techniques (e.g., Surface-enhanced Raman spectroscopy) and commercially available VOC detectors (e.g., PID, FID) as it provides comparatively better selectivity, reversibility, fast multiplexing features with elimination of electromagnetic interference, and portability.[87] The detection mechanism of optical sensors relies on the following properties of the electromagnetic waves: wavelength, phase, amplitude, intensity, and state of the polarization.[88] Recent advancements in optical sensing tools have concentrated on surface plasmon resonance (SPR), Bragg's fiber, colorimetric, Fabry–Perot cavity (FPC), and fiber optic based sensors.[89] Plasmonic sensors are potential for VOC sensing owing to their high sensitivity.[90] They were achieved by enabling the identification of extremely small wavelength shifts in an order of 10^{-3} nm via noble metal nanoparticles extinction spectra (absorption and scattering). This minute shifting has been controlled through the alteration of size, shape, and assembly of the nanoparticles and the ambient refractive index (RI).[91] The working mechanism of SPR affinity VOC sensors depends on the change of RI, formed by the capture of VOC molecules following the concentration gradient at the thin-film surface and their interaction.[92] The sensor response is proportionate to the alteration of binding-induced refractive index (n), where

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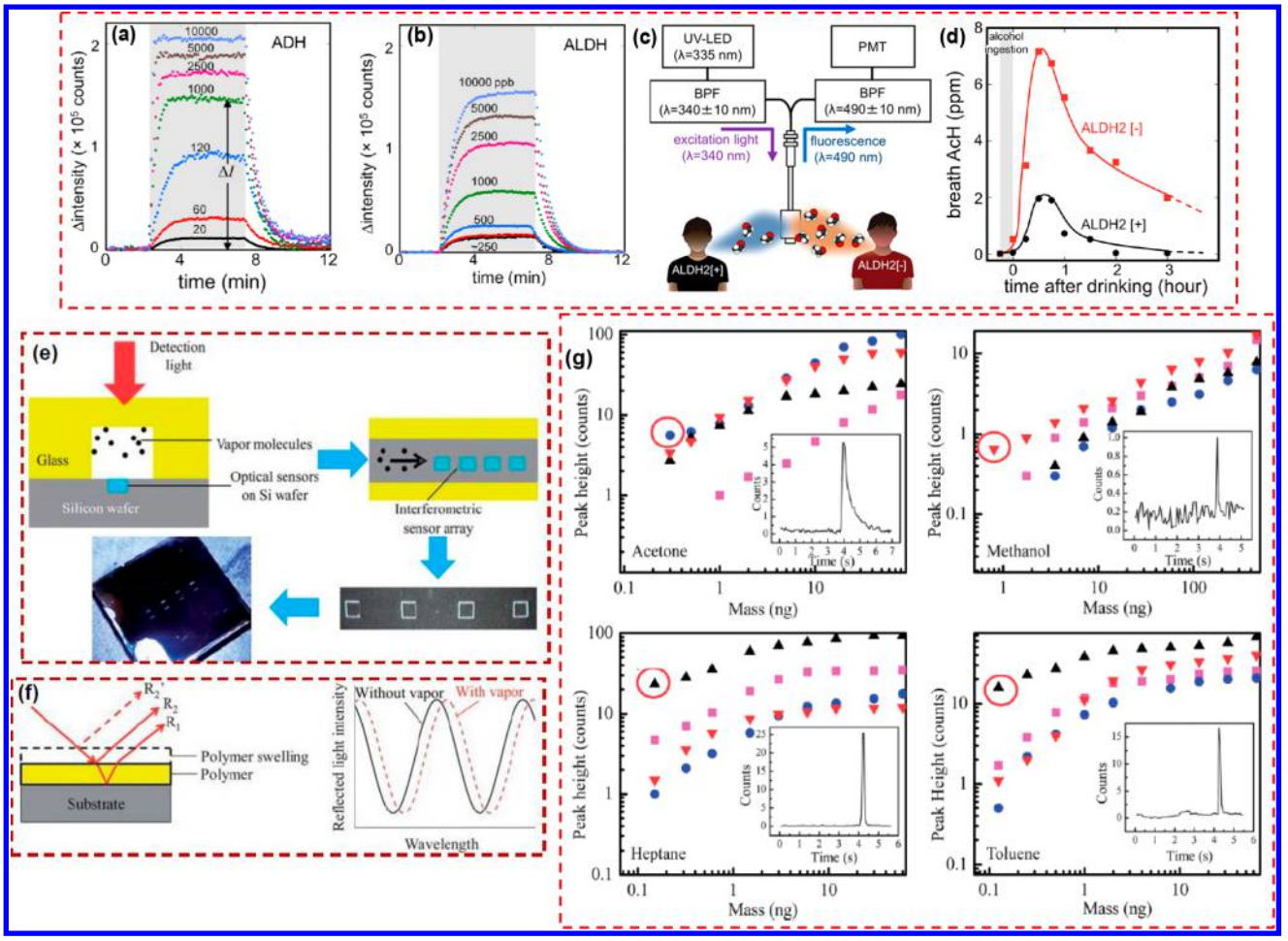

Figure 2. Responses of (a) ADH-mediated and (b) ALDH-mediated fiber optic biosniffer to different concentrations of AcH.[96] (c) Bifurcated fiber optic biosniffers setup to the ALDH2[+] and ALDH2[−] subjects[96] and (d) their time course of concentration of breath AcH after drinking which is about 3-fold difference at the concentration level.[96] Adapted with permission from ref 96. Copyright 2018 American Chemical Society. (e) Cross-sectional view of the FP sensor array (top left), top-view of the FP sensor array (top right), image of an etched silicon chip containing the sensor array (bottom right), image of four wells on chip (bottom left),[98] (f) principle of the Fabry−Perot cavity (FPC) sensor and interference pattern generated by an FP sensor and the effect of analyte absorption absorbance properties of light,[98] and (g) chromatographic responses of four FP sensors to a mixture of acetone, methanol, heptane, and toluene.[98] Adapted and reprinted in part with permission from ref 98. Copyright 2012, The Royal Society of Chemistry.

the binding occurs within this thin film at the sensor surface of thickness (t). The relationship can be expressed as[93]

$$\Delta n = \frac{\mathrm{d}n}{\mathrm{d}c}\,\frac{\Gamma}{t} \tag{8}$$

where, $\frac{dn}{dc}$ is the increment of RI with the concentration of analyte molecules and Γ denotes the surface concentration in mass/area.

Cheng et al. demonstrated reversible and highly sensitive localized surface plasmon resonance (LSPR) based sensor for the detection of toluene, *n*-octane, chlorobenzene, pentanol, and *m*-xylene. In their work, Ag-nanoparticles and Au-nanoshells enhanced the surface area which promoted significant adsorption of VOCs.[94] Chen et al. modified the thin film surface made of Ag-nanoparticles with thiolate self-assemble monolayer enhanced the VOC-selectivity and reversibility.[95] Iitani et al. demonstrated fluorescence based fiber optic biosniffers for the detection of acetaldehyde (AcH) from exhaled breath.[96] These biosniffers were calibrated with two different enzyme mediated environments: alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), which make the sensor selective for AcH. It was operated over a wide dynamic range from 0.02 to 10 ppm which covered the physiological range of breath AcH (1.2−6 ppm) and showed rapid response (≤100 s), as shown in Figure 2a and b. In another study, it was seen that ALDH2 extensively dominates the metabolic oxidation of AcH into acetic acid, with about 40% of Asians known to have lower metabolic action of ALDH2 (ALDH2[−]) than the others (ALDH2-[+]).[97] The bifurcated fiber optic biosniffers (Figure 2c) could distinguish from ALDH2[−]) to (ALDH2[+] by 3 times greater signal, as shown in Figure 2d. Contrarily, Reddy et al. developed a hybrid FPC sensor for VOC detection on a microfabricated chip functionalized with μ-GC, employing a vapor sensitive polymer on the substrate, as shown in Figure 2e.[98] The sensing mechanism relies on the alteration of refractive index with the concentration of VOCs (Figure 2f). The presence of the VOC in the polymer alters its thickness, which in turn changes it refractive index and shifts the wavelength to the degree of vapor sorption (Figure 2g). The kinetic and quantitative information on VOCs are obtained through the wavelength shifts inside the microfluidic channel.

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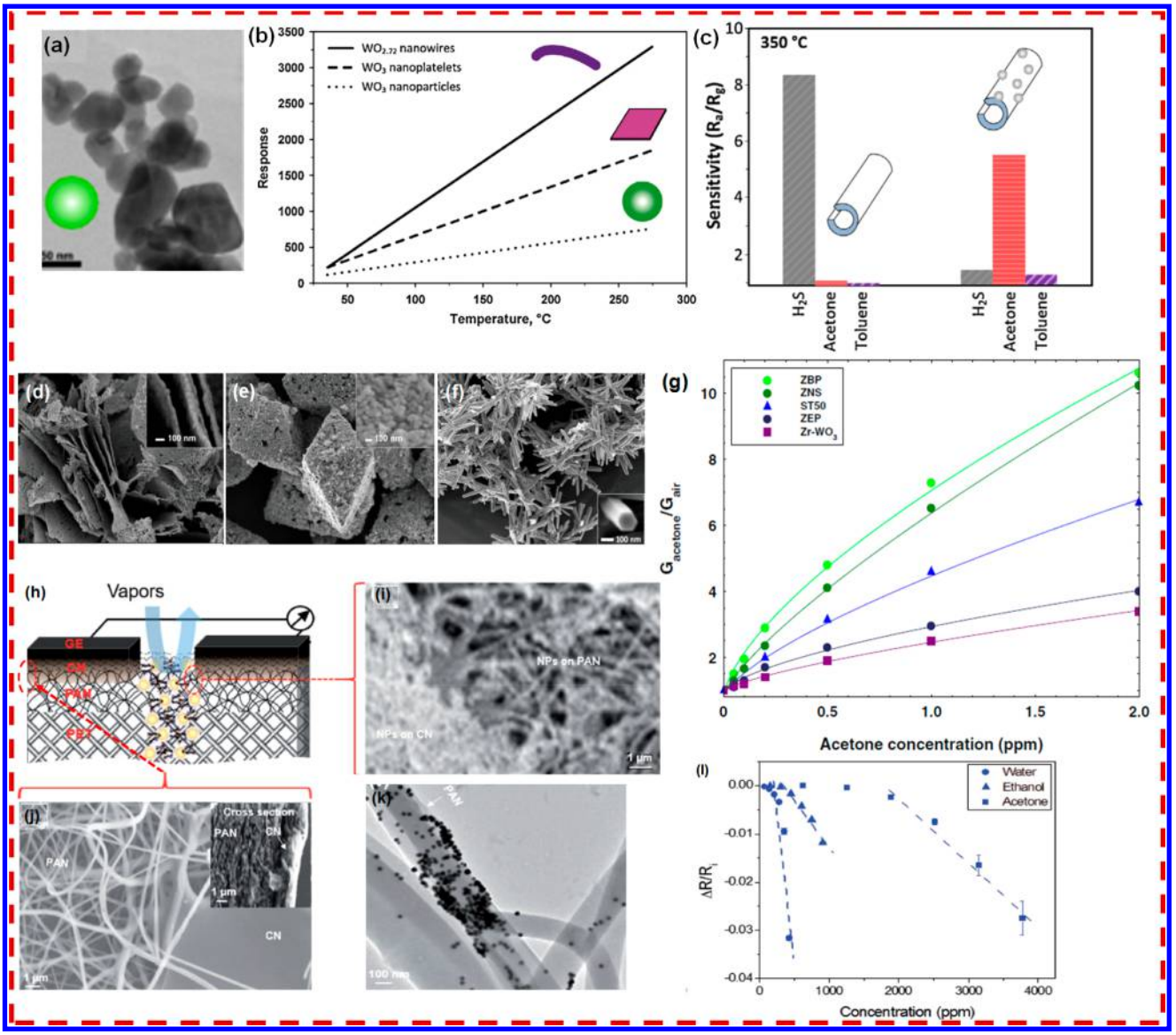

Figure 3. (a) SEM image of WO_3 nanoparticles,[110] (b) WO_3 based sensor response to 1000 ppm of H_2S for different structures as a function of temperature,[110] (c) H_2S and acetone response characteristics of WO_3-based sensor.[110] Reprinted with permission from ref 110. Copyright 2014 Elsevier Ltd. SEM images of (d) ZNS, (e) ZBP, and (f) ZEP. (g) Acetone response characteristics for different nanoparticles based sensors.[111] Reprinted with permission from ref 111. Copyright 2016 Elsevier Ltd. SEM and TEM images (h–k) of the nanofibrous paper and schematic of nanofibrous paper based sensor,[116] and (l) the sensor response sensitivities (ppm (M)): water (-1.9×10^{-4}), ethanol (-1.5×10^{-5}), and acetone (-1.1×10^{-5}).[116] Reprinted with permission from ref 116. Copyright 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In the work of Reddy et al., chromatographic responses of four FPC sensors were grating sensors, μ-ring resonator sensors, and photonic crystal obtained (Figure 2g) from a mixture of acetone (1), methanol (2), heptane (3), and toluene (4). Scholten et al. also developed an on-chip μ-ring resonator integrated with fluidic connections and optical fiber probes for sensing five different kinds of VOCs. Their findings revealed five different peaks confirming the level of sensitivities in the following order of ethylbenzene, toluene, perchloroethylene, isopropyl alcohol, and heptane, respectively.[99] Contrarily, Mu mentioned a bioluminescent bioreporter integrated circuit technique for detection of breath toluene from bioluminescent bacteria, through the translation of biochemical energy to photonic energy. Though this method limited the target analyte being to specific bacteria with very low (10 ppb) limits of detection (LoD), its longer response time (few minutes to hours) proved to be a hindrance to real-time monitoring.[88] Thus, the specific detection of a single analyte on a miniaturized scale with development of a single optical sensor is a challenge. Therefore, Mazzone's group demonstrated colorimetric sensor array combined with prediction model to diagnose lung cancer. In their study, they collected 229 subjects' data and diagnosed 92 individuals as carcinogenic patients with the accuracy of 0.8 C-statistics.[100] A portable breath analyzer based on colorimetric detection that analyzed the data, processed it and communicated the information to the user via a cell phone for selective nitric oxide sensing in ppb level (~50 ppbv) was also reportedly devised by Prabhakar et al.[101]

Chemiresistive Sensors. Different monolithic metal oxide based chemiresistive sensors have been receiving attention due to their high potential for miniaturization to develop portable

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and wearable diagnostic tools. The operating principle of these sensors relies on variation of resistivity with the depletion layer due to redox reaction, adsorption, and surface chemical reaction of analytes.[102] The width of the depletion layer is either reduced or increased in the n-type metal oxide. The commonly used n-type metal oxides, namely, tin oxide (SnO_2), tungsten oxide (WO_3), and zinc oxide (ZnO), are widely used for VOC sensing.[103] In the absence of VOC molecules, the presence of atmospheric oxygen species O^-, O_2^-, or O^{2-} attributes electrons which increase the depletion layer and resistivity, and vice versa. The relationship in between of reaction mechanism and electrical signal can be expressed by Langmuir−Hinshelwood equation as follows:[104]

$$S(t) = S_{max}\frac{C_{voc}K}{1 + C_{voc}K}\left[1 - \exp\left(-\frac{1 + C_{voc}K}{K}kt\right)\right] \quad (9)$$

here S_{max} is the highest signal change in complete saturation, C_{voc} represents the concentration of VOC, K defines as the adsorption constant of the target compound, and k represents forward rate constant.

P-type (nickel oxide, cobalt oxide) and zeolite type MOS sensors are also used in detection of VOCs.[105,106] Zeolite based chemiresistive sensors were reported for different VOCs, such as NH_3, amine, SO_2, and different hydrocarbons and organic molecules.[107] The sensitivity and selectivity of any type of chemiresistive sensor depends on the film thickness and working temperature.[102] Song et al. described a ZnO−SnO_2 nanofiber based ethanol gas sensor operating at 300 °C, providing high response, excellent linearity in the range of 1−300 ppm, quick response time (5 s) and recovery time (6 s), good reproducibility, stability, and selectivity.[108] Different metal oxide nanowires and ferroelectric WO_3 nanoparticles have been utilized for selective acetone sensing in breath-simulated media.[106] Choi et al. demonstrated a catalyst functionalized method using metal nanoparticles (Pt) incorporated with WO_3 hemitubes for highly sensitive acetone sensing at the operating temperature 250−350 °C.[109] In their work, Pt-functionalized WO_3 hemitubes exhibited superior acetone sensitivity in the presence of H_2S. Righettoni et al. also performed in-depth studies on the detection of acetone in exhaled breath using Si-doped WO_3 nanoparticles (Figure 3a) for the diagnosis of physical conditions including halitosis and diabetes.[110] In his work, it was clearly inferred that nanowires response is greater than nanoparticles and nanoplatelets as a function of temperature for H_2S (Figure 3b). He also demonstrated thin-walled WO_3 hemitubes made by polymeric fiber-templating based sensors operating at 350 °C for the diagnosis of halitosis and diabetes, detecting H_2S and acetone (∼120 ppb) respectively (Figure 3c).[110] Similarly, Fioravanti et al. demonstrated sub-ppm level acetone sensing with several metal oxide materials: several ZnO nanoparticles (ZnO bisphenoidal nanoaggregates, ZBP; ZnO nanosheets, ZnS; ZnO hexagonal prisms, ZEP), aggregated ZnO nanostructures with Zr-loaded WO_3, and TiO.5SnO.5O_2, where ZnO nanoparticles-based sensors exhibited better sensitivity than others (Figure 3d−g).[111] Employing vanadium pentoxide (V_2O_5) nanobelts, Liu et al. improved the performance of selectivity to ethanol in a multivariate environment at relatively low temperatures (150 °C) to save the overall power consumption.[112] However, most of these chemiresistive sensors require homogeneous and high temperature to operate.[113,114] Moreover, semiconductor metal oxide-based sensors are more prone to interference and contamination in VOC detection. Portable cost-effective breathalyzers (e.g., Figaro, Ketonix, BACtrack) are also commercially available for alcohol and acetone detection; meanwhile, wearable chemiresistive sensors are still a challenge. Recently, Tayebi et al. has reported monolithic, microfabricated sensor arrays comprising different metal oxides, allowing independent temperature controls and readouts for VOC sensing on a wearable platform.[115] Though many breathalyzers are chemiresistive-based, their high operating temperature and power management are key obstacles yet to overcome for design on a wearable platform.[113] Yan et al. illustrated nanofibrous paper based chemiresistive sensor fabricated with dendronized nanoparticles that show structurally tunable and negative signals in the presence of ethanol and acetone at room temperature (Figure 3h,i).[116] In their work, the electrical properties of the nanofibrous membrane matrix with dendronized nanoparticles are harnessed for exploring the multiple hydrophilic/hydrogen bonding sites in a 3D structural edge for sensing applications in humidity leading atmosphere such as human breathing or sweating.

Electrochemical Sensors. Electrochemical VOC sensors are considered among the most promising types of VOC sensors for wearables today. Electrochemical sensors work on the principle of redox reactions which target analytes undergo to produce measures which correlate with the concentration of the analyte.[89] These sensors can be classified as voltammetric, amperometric, or potentiometric. These kinds of techniques are most compatible for wearable sensing due to the ease of fabrication and miniaturization, rapid response, high accuracy, wide range of detection, biocompatibility, and low power consumption.[102]

Portable electrochemical sensors like breathalyzers available for alcohols, aldehydes, acetones, and isoprene. Portable halimeter (114 × 254 × 267 mm^3/3.6 kg) is popular for VSC (volatile sulfur compounds, e.g. hydrogen sulfide, methyl mercaptan, other thiols, and dimethyl sulfide) sensing for chronic halitosis following the electrochemical voltammetric technique which shows a detection limit of 5 ppb with response time of 1 s.[117] Apart from this, fuel cell based miniaturized and portable alcohol breathalyzers are popular and widely used for driving under the influence (DUI) cases in real-time, but cannot be used for continuous measurements.[22,118] Obermeier et al. reported integrated e-noses with three different amperometric sensors for detection of aldehyde, NO, and CO at sub-ppb levels for the diagnosis of lung cancer and treatment of those succumbing to oxidative stress.[119] Electrochemical sensing techniques have also been reported for continuous monitoring of propofolin exhaled breath of patients under anesthesia.[120] However, miniaturization is essential for the embedded sensing device in continuous monitoring and POC wellness management. A significant advancement toward wearables for continuous monitoring of alcohol from sweat or skin perspiration was achieved in the last few decades. Field trials of the sweat patch identified problems with ethanol collection and storage, evaporation loss, back diffusion, and bacterial metabolism.[121] Giner's wrisTAS and SCRAM CAM bracelet offers partially instantaneous (5 min to 2 h. interval) alcohol monitoring, through skin perspiration, using electrochemical sensors.[121,122] These anklet and bracelet based transdermal blood alcohol content (BAC) monitoring devices are used in semi-real-time and continuous manners for preventing DUI and for

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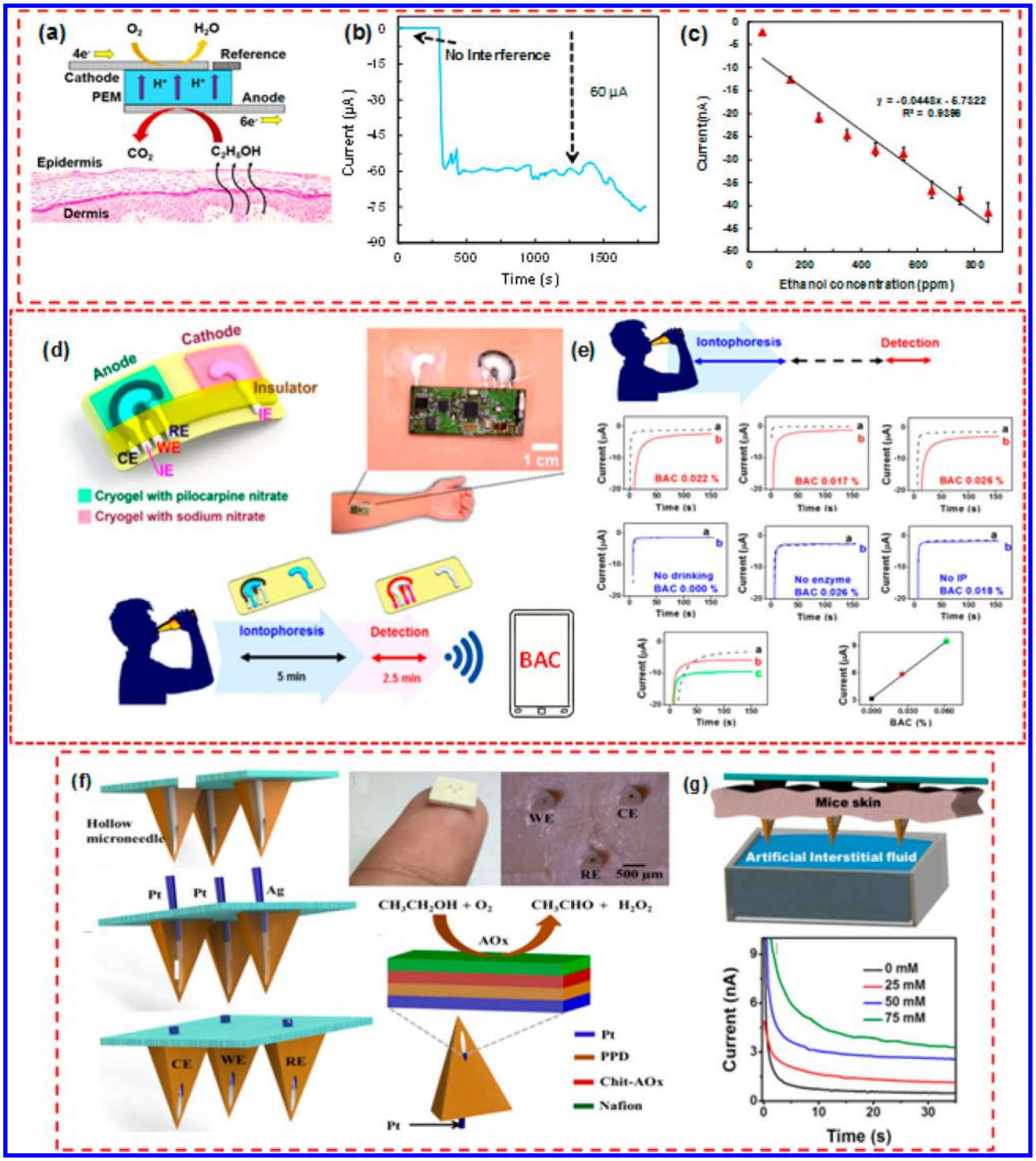

Figure 4. (a) Alcohol fuel cell sensing mechanism,[22] (b) elimination of humidity interference during ethanol detection,[22] and (c) amperometric response for ethanol detection.[22] Reprinted with permission from ref 22. Copyright 2017 Elsevier Ltd. (d) Tattoo-based transdermal alcohol sensor and (e) its responses.[122] Reprinted with permission from ref 122. Copyright 2016 American Chemical Society. (f) Schematic representation of microneedle based chronoamperometric sensor and (g) its responses.[123] Reprinted with permission from ref 123. Copyright 2017 Elsevier Ltd.

rehabilitation purposes. Bhansali's group also demonstrated nickel catalyst based fuel cell sensor for transdermal alcohol detection in wearables with a minimum detection limit of 5 ppm, eliminating the humidity interference (Figure 4a–c).[22] Kim et al. demonstrated integrated wearable epidermal tattoo-based amperometric biosensors with flexible iontophoretic sensing electrodes to improve the time in detection (Figure 4d,e).[122] This new, skin-worn, low-cost, noninvasive alcohol monitoring device enables real-time alcohol measurements in sweat. BAC can be calculated from the following relationship:[122]

$$\text{BAC (g L}^{-1}) = 0.71 \times \text{sweat ethanol concn (g L}^{-1}) \quad (10)$$

where $r = 0.912$.

Mohan et al. demonstrated a microneedle-based enzymatic electrochemical sensor for minimally invasive, continuous

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Table 1. Comparative Analysis of Different Sensing Methods

sensing method	target VOC(s)	biofluid types	physiological ranges of target VOCs	VOCs composition	detection limit	response time	selectivity of sensors	purpose
32 chemiresistors (organic polymer)[124]	pentane, isoprene, acetone, benzene	breath		874			accuracy of 85%	lung cancer
Colorimetric sensor array[100]		breath		874		5 min	accuracy: C-statistic 0.825−0.890	lung cancer
electrochemical (microneedle)[123]	ethanol	interstitial fluid (synthetic)	≤17 mM (max legal limit)	154	5 mM	30 s	selective via AOx enzyme	DUI
electrochemical (iontophoretic tattoo based)[122]	ethanol	sweat	2 ppm (normal)	532	52 ppm	7.5 min	selective via AOx enzyme	DUI
electrochemical fuel cell[119]	aldehydes	breath	2.2 ppb	874	1.5−25 ppb	22 s	moderately selective (interference compounds: ethanol, isopropanol, acetone, isoprene, propofol)	lung cancer/diabetes
chemiresistive[110]	acetone	breath	300−900 ppb (healthy) ≥ 1800 ppb (diseased)	874	∼20 ppb	<30 s	selective over ethanol and water	diabetes
chemiresistive[125]	ammonia	breath	∼0.8 ppm (healthy) 0.85 ppm −14.7 ppm (diseased)	874	50 ppb	∼ms to s	highly selective (using α-phase MoO_3)	lung/kidney/renal diseases
chemiresistive[126]	acetone, toluene	breath	300−900 ppb (healthy) ≥ 1800 ppb (diseased); toluene: 20−30 ppb (healthy) 80−100 ppb (diseased)	874	acetone: 35 ppb to 3 ppm; toluene: 1 ppb to 10 ppm	7.8 s	incorporating PVDF, PS, and PMMA nanofibers with MWCNT based sensing microchannel exhibit high tolerance to interfering VOCs	asthma, lung cancer, COPD, breast cancer
chemiresistive[127]	H_2S	breath	0.1−0.5 ppm	874	<0.1 ppm	15 s	highly selectivity to H_2S over CO, NH_3, CH_3COCH_3, C_6H_6, $CH_3C_6H_5$, $(CH_3)_2C_6H_4$, and NO at 300 °C	halitosis
optical (fiber optic biosniffers)[96]	AcH	breath	1.2−6 ppm	874	0.02−1 ppm	≤100 s	selective to AcH via ADH and ALDH	pharynx and tongue cancer
electrochemical (pilocarpine iontophoresis technique)[128]	ethanol	sweat	0.0005−0.6 g L^{-1}	532	0.0028−0.042 g/L	5 min	selective through alcohol oxidase/horseradish peroxidase (AOD/HRP)	clinical, occupational, and DUI (safety)
electrochemical[121]	alcohol	skin perspiration	0.02−0.08 g/dL	532	≤0.08 g/dL	2−5 min	selective to acetone and oxygen	forensic monitoring, abuse treatment

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monitoring of alcohol from interstitial fluid (ISF). Their three-electrode microneedle sensor comprised Pt and Ag wires with the Pt-wire functionalized with the alcohol oxidase (AOx) enzyme and a perm-selective reagent layer (Figure 4f). The sensitivity of this sensor is known to be 0.062 nA/mM having a correlation coefficient of 0.9886 (Figure 4g).[123]

An overview of sensing techniques, target VOC(s), and their availability in biofluids are listed in Table 1.

CHALLENGES AND SOLUTIONS FOR PRECISE DETECTION OF VOCs IN REAL-TIME

Clinical diagnosis of VOCs faced several challenges associated with the detection of ultralow concentrations of target molecules in a collective, complex multivariate environment. The development of continuous monitoring of VOC sensors faces several challenges in many respects, mostly from the following major fronts: (i) standardizing sensors' calibration, (ii) development of wearable devices, (iii) complexities of metabolism and VOCs' kinetics in a multianalyte system, and (iv) inter/intraperson variability of VOCs' profiles in such varied environments. Human anatomy and physiology is not identical; therefore, standardization of a generic sensing device for specific VOC detection is critical. For the same person, the pharmacokinetics and kinetics of different VOCs can differ from time to time depending on diet, drug consumption, body temperature, ambient environment, and physiological condition. Moreover, most sensors are influenced by the fluctuation of these ambient parameters and exogenous compounds that generate false positive readings.[22,122,129] The performance of a sensor degrades with time due to aging effect, contamination, corrosion of materials, and alteration of internal properties due to chemical or physical variables (e.g., temperature, humidity, pressure, etc.).[22,105,122] Different sensing parameters, such as reliability, sensitivity, selectivity, stability, and reversibility, are crucial in implementing the design of the sensor in wearable platform. The major challenges and their possible solutions on major parameters of different VOC sensing in humans are described below.

Sensitivity. Precise detection of low concentration is always a challenge in VOC sensing. Different analytical techniques are widely used in breath analysis to trace sub-ppm concentrations of VOCs.[9,10,130] Solid-state chemiresistive, optical and electrochemical sensors have also attracted attention in VOC detection due to their miniaturization and portability, higher sensitivity, and detection limit. The sensitivity of the sensor can be measured as in eq 12 below:

$$S = \frac{R_{air} - R_{gas}}{R_{air}} \times 100 \tag{11}$$

where R_{air} and R_{gas} are the sensor resistances in normal air and under gas.

Bur et al. improved sensitivity through platinum gate gas-sensitive SiC field-effect transistor (SiC-FET) having a detection limit of ∼1 ppb for benzene and naphthalene and ∼10 ppb for formaldehyde in humid atmospheres.[131] Barsen and Weimar developed screen printed ceramic MOS sensors which achieved detection limits as low as at sub-ppb levels, utilizing the recognized grain boundary effect.[132] Different amplification protocols that target recycling and proper selection of transducers have also been seen to improve the sensitivity and detection limit. The use of nanoparticles in different forms such as nanowires, nanoflakes, nanorods, nanofibers, nanotubes, nanospheres, and other nanostructures reportedly improves the sensitivity manifold in VOC sensors by increasing the surface area to improve detection. Modifying the nanoparticles and pore size in the synthesis of nanocubes and nanorods of SnO_2, Kida's group improved the sensitivity to 5 orders of magnitude in response to 100 ppm of ethanol on an optical sensing film.[133] Recently, Marques and McKnight referred the sensitivity of alcohol monitoring devices: SCRAM for transdermal alcohol content (TAC) was 65.3% and 86.5% for 0.02 and 0.08 g/dL concentrations, respectively.[134]

Selectivity. Cross-selectivity of sensors in a multivariate system is a prime concern in the detection of biomarkers. Nonspecific detection of the existing sensors can generate false positive error during measurements, from interactions with interfering compounds.[122,129] For example, anbesol, containing benzyl alcohol, is an anesthetic oral pain relief gel used to treat toothaches and canker sores that can yield a positive BAC reading. To improve the selectivity of the VOC sensors, different approaches can be employed. Selective catalysts or nanoparticles can improve the signal-to-noise ratio in detection of the target VOC.[135,136] In some cases, the size, shape, and phase composition of the nanoparticles play a role in differentiating different VOCs.[137] Pure and Si-doped WO_3 nanoparticles based on chemiresistive sensors allow detection of acetone in ppb levels of concentration (∼20 ppb), with high signal-to-noise ratio.[110] It was found that Si-doping increases and stabilizes the acetone-selective ε-WO_3 phase, while increasing its thermal stability and sensing performance. Zhang et al. mentioned Ag-doped In_2O_3-activated sensors for selective detection of alcohol in the presence of acetone, formaldehyde, ammonia, and H_2 at low temperatures.[138] Cr_2O_3 nanoparticle based chemiresistive sensors are also known to have shown a better response to NH_3 in the presence of other VOCs of higher concentrations at room temperature.[103] Doping of specific metal molecules in various metal oxides improves selective detection of some VOCs.[106] Lanthanum doped nanocrystalline thin-film of $LaFeO_3$ demonstrated excellent selectivity and stability for detection of ethanol in the transdermal range.[139]

Polarity is another important factor that plays a role in VOC sensing, while polar and nonpolar VOCs are selective to specific catalyst materials. The catalyst sensing element itself or the thin film of functionalized nanostructures on the sensing element can easily react with the polar compound through charge transfer and avoid reactions with nonpolar VOCs.[140] For example, a thin layer of self-assembled polycyclic aromatic hydrocarbon (PAH) covering RN-CNT chemiresistive films could discriminate between polar and nonpolar VOCs in a controlled environment. Using pulsed laser deposition (PLD), morphology of highly porous sensing layers has been known to contribute toward enhanced selective detection of naphthalene.[141] Second, a different dynamic approach can improve selectivity of VOC sensors. For example, temperature cycled operation (TCO) is accepted as a vigorous and adaptable technique, especially in chemiresistive sensors where a certain temperature window is dedicated for specific types of compounds.[142] A mixture of carbon monoxide, hydrogen, and selective sorbent material (e.g., Tenax, Car bopack X, Carboxen) is known to have the ability to entrap specific VOCs through thermal desorption (TD). Though the mentioned approaches improve selectivity, the detection of a specific compound from multianalyte system requires more robust techniques.

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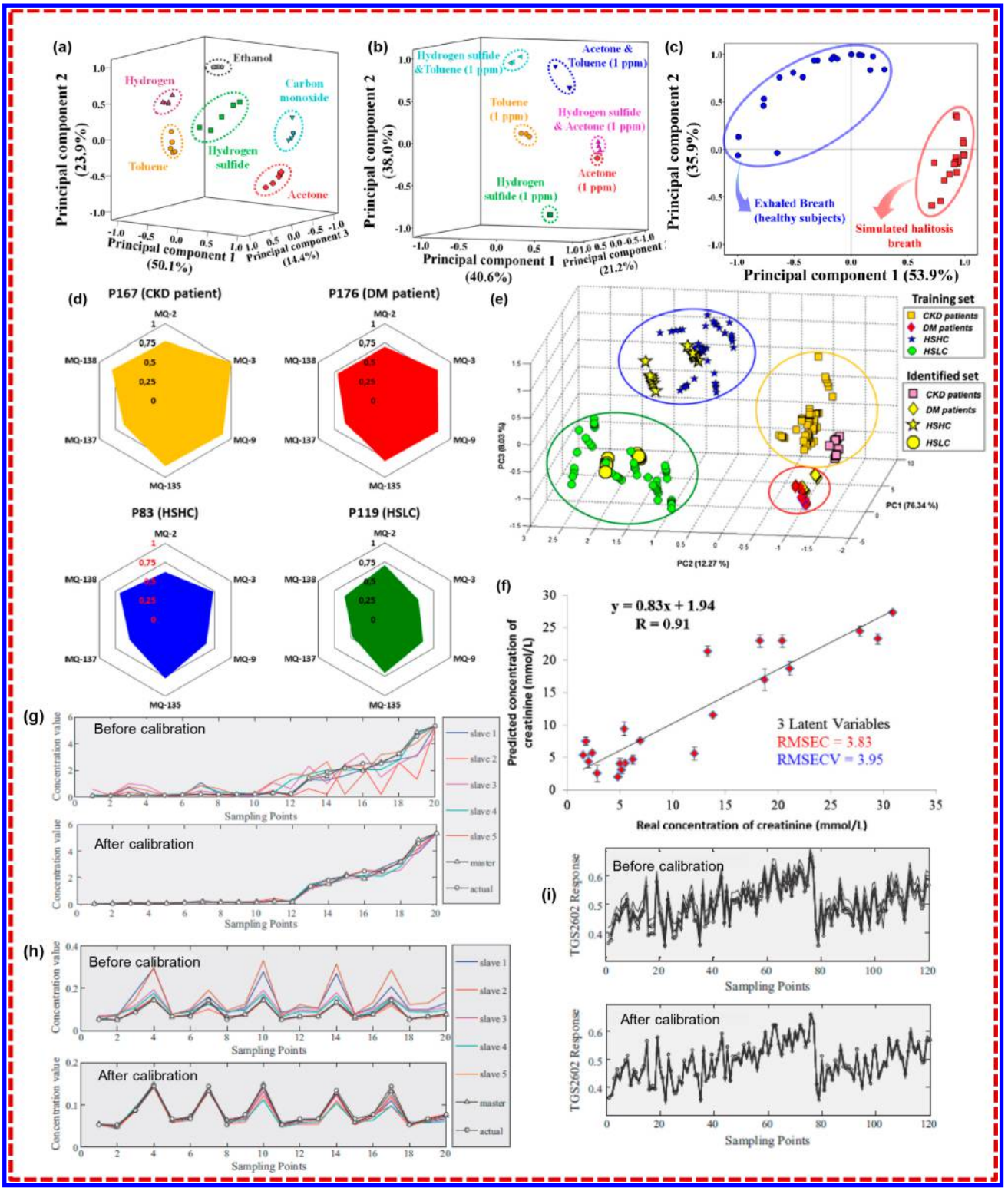

Figure 5. (a) Application of PCA for multiple biomarkers classification,[27] (b) classification of their mixtures using PCA,[27] and (c) classification between simulated halitosis breath and healthy human breath.[27] Reprinted with permission from ref 27. Copyright 2017 American Chemical Society. (d) Radar plots of four breath samples expressed as the area under conductance of temporal responses gathered from e-nose for CKD and DM patients and healthy subjects,[28] (e) PCA model built using the first set of measurements and fitting of second data sets onto the clusters,[28] and (f) PLS prediction model for creatinine content in the urine.[28] Reprinted with permission from ref 28. Copyright 2018 Elsevier Ltd. (g) TGS2602 responses with 120 samples measured before and after calibration, Performance of predicted concentrations on test samples (before and after calibration): (h) formaldehyde and (i) benzene.[152] Reprinted with permission from ref 152. Copyright 2011 Elsevier Ltd.

Recently, data mining and pattern recognition techniques have become popular and established tools to interpret data sets from a multidimensional environment, with precise measurement and classify cation of the volatile compound

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being measured. For precise calibration, the system needs to have multiple wearable "e-noses". Therefore, large and diverse data sets can be acquired based on diurnal activities and performances of the wearer. After acquiring the raw data from multiple input systems, it needs to be processed using machine learning or deep learning tools. These tools are suitable to train the algorithms on dependent and independent variables and provide a desired estimation for a precise calibration model for individual VOCs.[143] Different machine learning tools, such as principle component analysis (PCA), canonic discriminant analysis (CDA), independent component analysis (ICA), discriminant factorial analysis (DFA), partial least-squares analysis (PLS), artificial neural networks (ANNs), support vector machine (SVM), and hierarchical cluster analysis (HCA) have been reported to be adopted for specific VOC detection.[26,28,27,29] However, once a method of prediction has been established, the predictive accuracy is obtained through cross-validation of all the data sets. Prediction model improves the correlation of the data sets and infers a pattern whereas regression technique provides specific concentration of unknown value of future data streams in real-time through fitting with this pattern.[22,30,144] Mazzone's group (Cleveland Clinic) demonstrated chemiresistive sensor array for the detection of lung cancer from exhaled breath.[124] They applied PCA and CDA techniques for the classification of malignancy and benignity of lung cells and SVM was employed to generate a prediction model from the data. Their sensors demonstrated a sensitivity of 71.4% and high specificity (91.9%) for lung cancer diagnosis. Similarly, Kim et al. studied WO_3 based (or its alloy) sensor arrays to understand the selectivity of acetone in the presence of H_2S, H_2, CO, ethanol and toluene (Figure 5a). In this study, the authors showed how a mixture of the VOCs could be selectively detected without interference employing PCA (Figure 5b).[27] They also showed how overlapped signals of healthy breath and halitosis breath could be differentiated using PCA (Figure 5c). Saidi et al. applied the PCA method for the classification of chronic kidney disease (CKD), diabetes mellitus (DM), healthy subjects with high creatinine (HSHC), and healthy subjects with low creatinine (HSLC).[28] The radar plot is derived from e-nose responses, which demonstrated a significant distinction in between of the four different patterns, as shown in Figure 5d. The PCA and SVMs results also presented a clear classification among the four groups. Moreover, this classification was further validated by analyzing 48 different samples from 8 new volunteers, which coordinated with the PCA model (Figure 5e). They also demonstrated the PLS model which shows significant correlation of 0.91 in between the e-nose results, as shown in Figure 5f.[28] Similarly, Philip et al. applied the fuzzy logic model for the prediction of breast cancer with improved accuracy to their previously mentioned findings.[145] These studies reveal the prospects of machine learning toward in situ detection of specific VOC in a multianalyte system.

Stability. The stability and shelf life of any VOC sensor are crucial parameters to consider when designing a sensor for POC application. These features affect a sensor's reliability, and any false readings can be generated because of its instability. Multiple parameters, like relative humidity or temperature, and operational conditions (e.g., applied voltage), can change the sensor's properties (e.g., impedance) in real-time. Hence, most of the VOC sensors require manual calibration or additional controlling equipment during measurements. However, wearable sensors are concerned with detection at sub-ppm or ppb levels in real-time. In an environment where humidity, pressure, and temperature change erratically, a minute's change of humidity, pressure, or temperature can cause significant variation in the signals that affect the calibration of a sensor. Potyrailo established humidity and temperature as factors that can affect the calibration of methanol and ethanol in detection.[146] Similarly, the signals of a fuel cell sensor depend on humidity and temperature directly.[22] Additionally, other intrinsic or extrinsic properties of the sensors, such as structure alteration, phase conversion, poisoning, degradation, bulk diffusion, or interference may cause shifts in the baseline signal of the sensor with time.[147] Moreover, continuous exposure of any VOCs may instigate fouling effects, chemical alteration, and hysteresis (irreversible) nonspecific adsorption on the sensor surface.[148]

Different approaches were considered to improve the stability. Deng et al. demonstrated improvements in stability of thermodynamic properties of known unstable sensing materials (molecularly imprinted polymer, MIP) for a quartz tuning fork (QTF) sensor.[149] This has been reported through modification of MIP by mixing polystyrene. Their study showed the adsorption response increased with rising temperature for a new sensor, while it showed the opposite for an aged one. Their thermodynamic analysis on the calibrated data for VOC (e.g., *o*-xylene) demonstrated that a conversion takes place from endothermic to exothermic reaction through the alteration of MIP which improves its stability and aging effect. Contrarily, different thermally stable metal oxides, such as ZnO, SnO_2, TiO_2, WO_3, In_2O_3, TeO_2, and Co_3O_4 formed thin film nanostructures in SAW sensors to improve thermal stability through controlling chemisorption or redox reaction of the target VOCs at certain elevated temperatures. This temperature-dependent property also enhances sensitivity and selectivity for specific VOC.[15] However, Nguyen et al. mentioned Ti_nO_{2n-1} as a good catalyst to improve the stability of the ethanol fuel cell sensor.[150] Similarly, Pt is widely used as a catalyst in fuel cell sensing due to its high resistivity to corrosion, allowing a stable electrical response.[151] A multivaried sensing platform integrated with different e-noses can potentially improve selectivity and reliability, through various tools as mentioned earlier. This sensing platform acquires a multidimensional signature from diverse transducers collectively in which data is collected and processed using machine learning tools and pattern generation. Zhang et al. explored global affine transformation (GAT) and Kennard−Stone sequential algorithm (KSS) model for the calibration of SnO_2 based e-noses for formaldehyde and benzene sensing (Figure 5g−i).[152] The pattern matching relies on affine transformation which can be extracted from robust weighted least-squares (RWLS) algorithm and the Euclidean distance (d_z) of the samples in the subspace. To evaluate the performance, the root-mean-square error of prediction (RMSEP) and mean absolute relative error of prediction (MAREP) were calculated from eqs 12 and 13 as follows:

$$\mathrm{RMSEP} = \sqrt{\frac{1}{n}\sum_{n=1}^{N}(\varphi_n - T_n)^2} \tag{12}$$

$$\mathrm{MAREP} = \sqrt{\frac{1}{n}\left|\sum_{n=1}^{N}(\varphi_n - T_n)\right|} \tag{13}$$

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where φ_n and T_n denote the projected and real concentration samples for the nth variable, respectively. The applied algorithm eliminates the drifting effect and noise. Thus, any drift in response and interference issues can be minimized with desired quantification considering known parameters to affect the response.

CONCLUSION

VOCs as biomarkers provide a potential pathway for simple, direct, and effective monitoring of certain health conditions as discussed. However, challenges facing the field of wearable VOC detection were addressed in reliable calibration of a single biosensor. Sensitivity of the VOC sensors can improve significantly through the advancement of nanotechnology. However, specific detection by a single sensor from a multivariate surrounding is yet to be overcome in precise, accurate sensing for wearable applications. Most breathalyzer based devices show 20−40% of error, which make these devices inefficient. Simpson mentioned 90% of this ambiguity is due to biological variables of the subject, and at least 23% of subjects will have their actual BAC overestimated.[153] However, advancement of nanotechnology and micromachining promote integration of multiple sensing modalities on a single platform. The integration of e-noses in a multimodal sensing platform through sensor-fusion have helped to do away with certain issues of selective in specific diagnosis of a physiological condition of an individual. Pattern recognition and machine learning or deep learning tools have been being employed in multimodal sensing approaches via e-noses for precision and accuracy as aforementioned. Such prospects provide pathways for noninvasive detection of VOCs as biomarkers on a wearable platform for POC continuous monitoring and personal health management in real-time.

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Notes

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VOCABULARY

Volatile organic compound (VOC), diverse class of carbon backboned chemicals which significantly evaporate at room temperature and pressure; biosensor, device that transforms biochemical information, ranging from the concentration of a specific biological sample component to total composition analysis, into an analytically useful signal[7]; E-noses, sensor or sensors array which enables to diagnose the odor of specific VOC(s) via pattern recognition[154]; biofluid, liquid within the body, generated by metabolic or pathological process, which can be excreted, secreted, or obtained from the body with external suction tools; sensitivity, change in the sensor signal per change in the concentration input; selectivity, reflects the sensor's ability to discriminate between the target analyte and coexisting interfering components; stability, degree to which sensor performance and hence response remain constant over time

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