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Breath Sensors for Health Monitoring

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Abstract

Breath sensors can revolutionize medical diagnostics by on-demand detection and monitoring of health parameters in a non-invasive and personalized fashion. Despite extensive research for more than two decades, however, only few breath sensors have been translated into clinical practice. Actually, most never even left the scientific laboratories. Here, we describe key challenges that currently impede realization of breath sensors and highlight strategies to overcome them. In specific, we start with breath marker selection (with emphasis on metabolic and inflammatory markers) and breath sampling. Next, the sensitivity, stability and selectivity requirements for breath sensors are described. Concepts are elaborated to systematically address these requirements by material design (focusing on chemoresistive metal oxides), orthogonal arrays and filters. Finally, aspects of portable device integration, user communication and clinical applicability are discussed.

Keywords: breath analysis, chemical sensors, biomedical, nanoparticles, filters, sensor arrays, sampling, personalized medicine

Despite a growing diagnostic toolset and a plethora of preventative and therapeutic interventions, a major challenge remains the control of epidemic diseases like obesity, diabetes or cancer. Great promise bears the current transformation of healthcare from disease-reactive to *predictive*, *preventive*, *personalized* and *participatory* - the so-called "4P" medicine[1]. Breath analysis could play a key role in this by providing on-demand critical health data. In fact, human breath is rich in physiological information[2] and particularly attractive (1) in recognizing abnormal breath patterns indicating the early development of a disease[3] and (2) to guide and personalize disease therapy. This is especially promising for slowly progressing diseases with few early indicators (e.g., cancer[4], insulin resistance[5]/diabetes[6] or renal dysfunction[7]) and those where a variety of treatment options exists, however, with different and not easily predictable patient outcome (e.g., obesity[8] or cancer[9]).

For daily breath analysis in wide-spread populations, simple-in-use and portable breath detectors are required. For this purpose, chemoresistive sensors are quite attractive due to their compact design[10], low cost and low power consumption[11] being ideal for integration into handheld devices[12]. Such inexpensive technology has amazing point-of-care potential as breath markers, reflecting immediately physiological and pathological changes, can be detected repeatedly or even monitored continuously (similar to vital sign monitoring) without any burden for the patient. Also, it creates new opportunities for healthcare in low-income countries with scarce medical resources[13]. Despite extensive research efforts and exciting scientific discoveries in the last two decades, however, to date only few breath sensors have been translated into actual products. Most never made it beyond the laboratory stage failing usually on key requirements, such as, sufficient sensitivity and selectivity to detect breath markers accurately at trace-level concentrations.

This perspective highlights the exciting opportunities of breath sensors in medical diagnostics and monitoring. Particular focus is laid on challenges that currently impede their

successful implementation and strategies on how to overcome them. More specifically, we the breath sensor development by discussing breath marker selection and critical steps in sensor design with emphasis on chemoresistive metal oxides, arrays, filters, device integration and clinical applicability. This development is highly interdisciplinary involving engineering, medicine and natural sciences with challenges arising often at their interfaces.

Breath markers

Human breath consists of nitrogen, oxygen, carbon dioxide, water, inert gases and over 870 other compounds typically occurring at parts per trillion (ppt) to parts per million (ppm) concentrations[2]. Nowadays, only few breath tests are established in clinical practice, including the H_2 and CH_4 test upon ingestion of carbohydrate substrates (e.g. lactose[14] or fructose[15]) to indicate intolerances and bacterial overgrowth in the small intestine[16], CO_2 monitoring in intensive care and anesthesia[17], O_2 and CO_2 analysis for indirect calorimetry[18], $^{13/14}C$ urea test for the diagnosis of *Helicobacter Pylori* infection[19], FeNO to detect asthma[20] and the ethanol tests employed by law enforcement[21]. For routine health parameter measurement, endogenous volatile organic compounds (VOC) are especially interesting as they reflect individual metabolic and inflammatory conditions[22]. However, to date only little is understood about most VOCs and their breath phenotyping is the focus of ongoing and intensive research.

New breath markers are identified typically by high-resolution mass spectrometry (e.g., secondary electrospray ionization mass spectrometry (SESI-MS)[23]) due to their bench-top sensitivity and selectivity. Compact sensors are developed usually in a second stage, when a compact breath test is required. Before starting the time-consuming development of a sensor, however, it should be carefully checked if the putative breath marker is sufficiently understood, including, at least, (1) a known biochemical pathway to clarify its origin and (2) sufficient clinical evidence ideally with multi-center confirmation. Too often, potential breath

markers have been proposed with insufficient evidence (e.g., for cancer detection) and without elucidating their biochemical origin.[24]

For metabolic monitoring, several candidates are attractive. Exhaled acetone, for instance, is one of the most abundant breath VOCs and produced in the hepatic mitochondria after fatty acid oxidation[25]. Usual breath acetone concentrations in healthy subjects are between 148 and 2744 parts-per-billion (ppb)[26] that increase during prolonged fasting[27] when shifting fuel preference from hydrocarbons to lipids[25]. Significantly elevated acetone concentrations (tens to hundreds of ppm) were observed in children[28] and adults[29,30] following ketogenic diets (high fat at low carbohydrate and low protein intake). Therein, breath acetone could reflect the individual status of ketosis[29], an important parameter to guide, for instance, the treatment of refractory epilepsy[31] or weight loss and optimize endurance performance training of athletes[32]. The highest acetone concentrations (hundreds of ppm) are observed in diabetic ketoacidosis[33]. Rapid breath acetone increases are obtained also during exercise[34] (with a maximum concentration at the aerobic lactate threshold[35]) and post-exercise rest in a fasting state (Figure 1a)[36] in good correlation with blood β-hydroxybutyrate (BOHB)[36,37]. Recently, acetone has been shown to be an important predictor of the post-surgical course after bariatric surgery[38]. Note, however, that a close correlation between breath acetone and glucose seems not to exist, as tested with 141 subjects after fasting and when undergoing an oral glucose tolerance test[39].

Figure 1

Exhaled isoprene from healthy adults is ranging from 22 to 234 ppb[40] but even lower levels can occur in children[41] and young adults[42]. Breath isoprene rapidly increases during physical activity (Figure 1b)[43] due to release from muscle tissue that probably serves as extrahepatic production and storage site[44]. Furthermore, it may be a by-product of cholesterol biosynthesis[45], and a correlation to blood cholesterol was proposed for patients undergoing treatment with cholesterol-lowering lova-[46] and atorva-statins[47].

Ammonia is an important breath compound occurring at relatively high concentrations in mouth-exhaled (248 - 2935 ppb)[26] and nose-exhaled (at around 100 ppb)[48] breath. Being a product of protein metabolism and toxic at elevated concentrations, endogenous ammonia is converted to urea in the liver and extracted via the glomerulus (urea cycle) or depleted by exhaled breath in healthy humans[49]. For impaired kidney function, ammonia is elevated in mouth-exhaled breath but decreases during hemodialysis treatment (Figure 1c)[50]. However, it should be noted that mouth-exhaled ammonia concentrations are dominated by enzymatic production from saliva in the oral cavity[51]. Therefore, elevated mouth-exhaled ammonia levels may be an indicator also for poor mouth hygiene[52]. Better correlation to blood ammonia levels may be obtained by ammonia measurements through nose-exhaled breath, though this needs to be investigated. Furthermore, ammonia levels increase when fasting after protein-calorie meals[53]. Also, abnormal ammonia levels have been related to hepatic dysfunction (e.g., cirrhosis,[54] hepatic encephalopathy[54] or hepatic injury[55]), halitosis[56] and bacterial infection by *Helicobacter Pylori*.[57] Having all these potential influences on mouth- and nose-exhaled breath ammonia levels, its clinical relevance needs to be carefully evaluated, as elaborated recently[52].

Exhaled breath contains also H_2 and CH_4 typically at concentrations below 20 ppm after overnight fasting[58]. They are produced through anaerobic fermentation of carbohydrates in the large intestine[59]. As a result, malabsorption of carbohydrates or bacterial overgrowth in the small intestine can drastically increase H_2 and CH_4 concentrations to several tens of ppm[58]. Also, a correlation between breath H_2 concentrations and pancreatic disease has been suggested recently[60].

Inflammation is the underlying pathological process of several diseases. Low-grade inflammation is present in chronic metabolic diseases as obesity, metabolic syndrome and diabetes[61]. Recently, anti-inflammatory therapy was shown to reduce the ultimate complication of metabolic diseases (e.g., cardiovascular disease[62]). Thus, it is important to

closely assess the effect of behavioural intervention and medical therapy on inflammation. This has not been accomplished so far since non-invasive measurement is not established. Breath analysis offers new opportunities to monitor inflammatory conditions non-invasively. In untreated asthma patients, for instance, elevated levels of NO[20,63,64] (Figure 1d), CO[65], ethane[66] and pentane[67] were reported. In addition, these markers have been correlated to other inflammatory disorders and oxidative stress in the respiratory tract such as chronic obstructive pulmonary disease (ethane, CO and NO)[68], cystic fibrosis (NO[69], CO[69] and ethane (Figure 1e)[70]), bronchiectasis (NO[69], CO[69,71]) and obstructive sleep apnea (NO and pentane)[72].

Breath sampling

Correct breath sampling is a pre-requisite for meaningful breath analysis[73]. Various factors may influence the breath marker concentration including breathing route (e.g., mouth vs. nose-exhaled[48]), exhalation rate[74], airway pressure[75], maneuvers like breath holding[76] or posture[77]. Furthermore, the choice of breath portion is an important decision. While early breath should be sampled if the marker of interest originates from the oral cavity (e.g., H_2S for halitosis[78]), end-tidal breath is particular interesting if the marker is blood-borne (e.g., acetone or isoprene)[43]. Breath portions can be sampled individually by geometrical separation (e.g., exhalation tubes[79]) or with CO_2-triggered valves[80]. As a result, all these factors need to be considered when designing a sampler for meaningful and reproducible breath analysis. So far, standardized protocols are available only for few compounds (e.g., NO[75]) while a task group of the International Association of Breath Research (IABR)[81] has been formed recently to standardize procedures also for other breath marker candidates.

Commonly applied in research is *offline* breath analysis where the sample is extracted and stored in Tedlar[82,83]/Mylar[84] bags, adsorption traps[85] or glass vials for liquid samples[86]. Analysis is performed offline in a later step that can be also at another location (e.g., a laboratory). This strategy appears particularly suitable if analysis devices are bulky and

affordable only in limited numbers (e.g., high resolution mass spectrometers) where sample analysis has to be centralized. Critical about this approach, however, is sample authenticity as analyte concentration may be affected by storage (e.g., diffusion through Tedlar[87]) and sampling containers can introduce contamination if not thoroughly cleaned.

More attractive for sensors is *online* breath analysis where the sample is analyzed instantaneously. This is required if immediate feed-back is desired, for instance, during physical activity to guide training conditions[36] or dieting at home. Originally developed for mass spectrometry[88], *buffered end-tidal* breath sampling is particularly suitable for sensors to meet their prolonged exposure times. Therein, breath is exhaled through an open-ended tube until the last portion is kept inside and *buffered*[88]. This concept has been tested successfully for gas sensors[36] and implemented readily in an industrial prototype for portable breath acetone detection[12]. Such breath samplers can be connected flexibly to different sensor types and applied for sampling of various end-tidal breath compounds (e.g., isoprene, ethanol, methanol and acetone)[79]. Flow restrictors are typically applied for a controlled and prolonged exhalation while visual prompting of the airway pressure can guide the subject to a target value for a reproducible exhalation[12]. Finally, exhalation flow and breath portion (through CO_2 detection) should be monitored to assess the exhalation process[79].

Sensor design

Sensors based on semiconductive metal-oxides (SMOx) are particularly suitable for hand-held breath analyzers due to their compact size and low cost[10]. To apply them for breath analysis, however, some requirements need to be met:

1. *Sufficient sensitivity* and *lower limit of detection* to sense breath markers at their trace-level concentrations.
2. *High selectivity* to accurately detect single breath markers against other compounds.
3. *Stability* during the operational period to ensure reproducible breath analyses.

These can be met by systematic design of the components and operational conditions of a sensor system (Figure 2) including sensing material, arrays and filters.

Figure 2

Sensitivity and lower limit of detection

The SMOx sensors are chemoresistive-type, in other words, they change their resistance when exposed to reactive gases[89]. Originally, such sensors were developed as alarm detectors for toxic (CO) or explosive (CH_4) gases[90] at elevated ppm concentrations. However, in breath analysis, markers occur typically at sub-ppm concentrations (e.g., isoprene[40]) and high relative humidity (RH, typically 89-97%[91]). Nanoscale engineering facilitates such lower limits of detection since sensor responses increase dramatically when decreasing the crystal size of sensing structures to twice their Debye length[92]. Further sensitization can be achieved by adding noble metals, dopants and foreign oxides and by morphology alteration, as reviewed recently[93].

Sensing nanoparticles are deposited conventionally by screen printing or doctor blading slurries or pastes resulting in rather compact films[94]. Extremely porous (typically > 90%[95]), crack-free[94] and highly pure films are obtained by flame-aerosol deposition. Therein, sensing nanoparticles are formed in the gas phase with well-controlled size[96], composition[97], phase[98] and morphology and directly deposited as fine network of agglomerates and aggregates by thermophoresis onto cooled electric circuitry[95]. Measuring the film resistance in situ during deposition allows monitoring of the sensing network formation and optimization of fabrication parameters to tune film morphology[99]. Such highly porous sensing networks are shown exemplarily by top view scanning electron microscopy (Figure 3a) of 2.5 mol% Ti-doped ZnO films[100]. The open and ultrafine structure of these films is beneficial for sensing as gas molecules can rapidly diffuse into the film and interact with the tremendous surface area of constituent nanoparticles. This results in high sensitivity to detect even the lowest but

breath-relevant analyte concentrations, e.g., 5 ppb of isoprene at 90% RH with fast response and recovery times[100].

Figure 3

In summary, sufficient sensitivity and lower limits of detection in the low ppb range can be obtained by nanoscale engineering of sensing films. Most progress is achieved by advances in fabrication technologies that systematically improve control over nanoparticle characteristics. When evaluating the sensitivity and lower limits of detection of new sensing materials for breath analysis, it needs to be emphasized that characterization has to be done at *breath-realistic conditions*, i.e. high RH[91] and relevant analyte concentrations in gas mixtures[2]. Too often, tests are performed with unrealistically high concentrations of single analytes at dry conditions. That way, the true value of a sensor for breath analysis can be hardly assessed.

Selectivity

Achieving sufficiently high selectivity is probably the most challenging hurdle when designing breath sensors. In general, selectivity is affected by sensing material design, arrays and filters (Figure 2). During the development of these components, selectivity may be tested *first* on single gases and simplified gas mixtures (simulating breath) to identify confounders. Ultimately, it needs to be demonstrated, however, in real breath with a statistically significant number of samples and comparison with bench-top technologies like high resolution mass spectrometers. The latter will be discussed in the section *clinical applicability*.

Material design

Selectivity is strongly influenced by the choice of material, in particular, its surface reactivity. While selective interactions between metal-oxides and certain analytes are well-known from heterogeneous catalysis, most applied sensing materials feature poor selectivity (e.g., SnO_2). Selectivity may be found in SMOx with unique composition (e.g., metastable

phases, solid solutions, mixed oxides, heterojunctions) or morphologies. State-of-the-art sensing fabrication methods, such as flame aerosol technology, are ideal to explore novel materials due to their flexibility in material composition[97] and superior control over particle characteristics (e.g., size[96], morphology, crystal phase[98]) at the nanoscale.

Selectivity may be found in specific crystal phases of a material. The α-phase of polymorphic MoO_3, for instance, features promising ammonia selectivity[101]. Addition of Si refines the MoO_3 structure by improving its thermal stability[102]. This enhances also its sensitivity to detect low ammonia concentrations down to 400 ppb at 90% RH, corresponding to low mouth-exhaled concentrations in healthy subjects[50], while selectivity over other major breath compounds (e.g., acetone, NO and CO) is improved as well[102]. Another example is the ε-phase of polymorphic WO_3 exhibiting high selectivity to acetone[103]. This metastable phase (stable below -40 °C[104]) is not accessible by conventional wet-phase techniques, but can be captured by flame aerosol synthesis of WO_3 when stabilized by Cr-[103] or Si-doping[98]. Acetone selectivity has been associated to the spontaneous electric dipole moment of ferroelectric ε-WO_3 that interacts with the dipole moment of acetone[103]. Even the exposed surface facet can affect selectivity. In fact, studies on hexagonal WO_3 have shown that nanorods with exposed (002) facets feature higher selectivity to acetone than those with exposed (001) facets[105].

Forming solid solutions, mixed oxides, metal-metal oxide composites and assembling them to distinct morphologies (e.g., surface clusters, p-n heterojunctions) can bring along synergistic effects to improve selectivity. For example, ZnO is a widely-applied sensing material with poor selectivity (Figure 3b). Adding only 2.5 mol% of Ti increases the responses to isoprene (black squares) by more than 15 times turning it isoprene-selective over acetone (red circles), ethanol (green triangles) and ammonia (blue diamonds)[100]. Doping ZnO with Ti leads to substitutional incorporation of Ti^{4+} into the ZnO lattice with increased density at the particle surface[100]. These Ti^{4+} surface sites feature strong interaction with isoprene, as revealed by *insitu* infrared spectroscopy[100].

High selectivity to H_2S is obtained by p-n heterojunctions of CuO and SnO_2 due to conversion of CuO to CuS upon exposure[106]. The H_2S is a constituent of malodor formed in the oral cavity from sulfur containing amino acids by anaerobic bacterial degradation[78]. Remarkable H_2S selectivity over other breath-typical confounders (e.g. ethanol, ammonia, CO and acetone) has been reported for porous WO_3 microbelts loaded with Pt catalysts (Figure 3c,d)[107].

Currently, single atom catalysts (Au[108], Pt[108], Ir[109] or Pd[110]) receive increasing attention in heterogeneous catalysis due to their unique activity which may exhibit also interesting sensing properties. While sensing materials are combined rather empirically, novel in-situ techniques (e.g., DRIFTS) enable systematic understanding of synergistic effects, as demonstrated recently with Rh_2O_3 clusters on WO_3[111].

Exhaled human breath contains high RH levels that may change dynamically (typically 89 – 97%[91]). Since RH interferes strongly with SMOx sensors, improving humidity robustness in sensing materials has been target of intensive research. To date, however, little mechanistic understanding exists about the effects of humidity on surface reactions. For SnO_2 sensors, it is known that humidity-related species (e.g., hydroxyl groups) occupy their surface and replace more reactive oxygen-related species resulting in reduced sensitivity for most gases[112]. For WO_3, on the other hand, humidity oxidizes the surface and can interact stronger with reducing gases (e.g., CO)[113]. There have been important advances in material design to remove the humidity dependence from SMOx sensors. Notably, it was demonstrated that Sb[114], Ti[115] and Tb[116] incorporation into SnO_2 inhibit the effects of RH by maintaining the state and concentration of surface-reactive oxygen species. However in case of Tb-doped SnO_2, this dramatically reduced gas sensitivity[116]. A more pragmatic approach is the application of humidity sensors that can compensate for RH dependence of SMOx[117,118].

Finally, the operational temperature of the sensor is a major parameter influencing its selectivity. In specific, the sensor response is determined by the surface reactivity of the

SMOx and the oxidation/reduction activity of the analyte[119]. When increasing the temperature of SMOx sensors, their responses go through maxima at optimal catalytic conditions that are found individually for each material-analyte combination[119]. As a result, operational temperature for optimal selectivity can be determined by evaluating the temperature-response profiles for the target analyte and confounders.

Despite decades of intensive material research, only few sufficiently selective sensing materials have been found and tested with real human breath in a statistically significant number of volunteers (e.g., Si-doped WO_3[36]). While sensor scientists tend to focus primarily on sensing material design optimization to overcome poor selectivity, other strategies may offer effective alternatives, as described below.

Sensor arrays

Combining differently-selective sensors to an array (Figure 2) and statistically processing their responses is a well-known option to overcome selectivity limitations of single sensors[120]. To give an example, formaldehyde has been proposed as one of the breath markers for lung cancer[121]. Typically, it needs to be detected at below 100 ppb[122] in the presence of other breath compounds (e.g., ammonia, acetone or ethanol) at significantly higher levels. To date, no single SMOx sensor provides sufficient selectivity. Combining moderately-selective Pt-, Si-, Pd- and Pt-doped SnO_2 sensors to an array and processing their responses with a multivariate linear regression algorithm[123] results in accurate formaldehyde detection (avg. error 9 ppb) in simulated breath mixtures (with significantly higher ammonia, acetone and ethanol concentrations) at 90% RH[124]. A similar approach[125] has been used for an array of four WO_3-based sensors with different response characteristics to discriminate eight breath-relevant compounds in simulated gas mixtures by principal component analysis (Figure 3e). With increasing gas mixture complexity, however, the estimation errors of arrays increase[124]. This is especially problematic for the breath with its hundreds of gases[2] where conventional

array designs based on rather collinear (i.e. similarly selective) sensors feature too low discrimination power resulting in insufficient accuracy.

State-of-the-art nanomaterial fabrication methods facilitate synthesis of sensing materials with distinct and different selectivities by exploiting unique material compositions and morphologies, as elaborated above. Combining such sensors to arrays increases *orthogonality* that result in improved discrimination power and thus accuracy[126,127]. Such rather orthogonal arrays perform well in real-world gas mixtures, for instance, when monitoring breath and skin emissions of entrapped humans in plethysmography chambers[118]. In fact, such an array consisting of distinctly selective Si-doped WO_3 (acetone), Ti-doped ZnO (isoprene) and Si-doped MoO_3 (ammonia) sensors together with commercial RH and CO_2 sensors detected even sub-ppm breath- and skin-emitted acetone, ammonia and isoprene concentrations with high accuracies (19, 21 and 3 ppb, respectively) and precisions, unprecedented by single SMOx sensors[118]. These results were in good agreement (Pearson's correlation coefficients ≥ 0.9) with bench-top selective reagent ionization time-of-flight mass spectrometry (SRI-TOF-MS)[118]. Therefore, such tailor-made sensor arrays with optimized orthogonality characteristics are quite promising to overcome selectivity limitations of single sensors and enable accurate multi-tracer assessment in breath analysis.

Sometimes, a so-called "black box" approach is applied for sensor arrays in breath analysis[84,128]. In an attempt to circumvent selectivity limitations for breath markers, sensor response patterns are correlated directly to the occurrence of a disease without identifying the underlying analytes. However, this approach bears the risk of pseudo correlations[129]. Sensor response patterns may be generated by confounders rather than actual breath markers, thus an association to the disease may not even exist. As an example, the "black box" approach for sensor arrays has been tested frequently on lung cancer patients[128]. However, a putative signal pattern may be generated rather by tobacco smoke residuals instead of lung cancer breath markers[130]. A correlation between signal pattern and the disease is obtained simply due to the

high likelihood that lung cancer patients are active or ex-smokers[130]. As a result, such "black box" breath tests should be viewed with caution.

Filters

Selectivity can be enhanced further with filters (Figure 2) that remove confounders (e.g., semi-permeable membranes), transform them into inactive species (e.g., catalytic filters) or retain them based on sorption properties (e.g., sorption columns). Particularly attractive is their greater flexibility to optimize selectivity, especially if its working principle differs from that of the sensor. For instance, sensing properties of SMOx are dominated by surface reactivity. As a result, species from the same chemical family (e.g., methanol vs. ethanol) can hardly be distinguished. Size-selective membranes (e.g zeolites[131]) introduce the ability to exploit also physical properties including molecular diameter. Drawbacks of filters are the increased complexity and costs of a sensing system, the potential reduction of sensitivity, increased response and recovery time if target analytes are compromised and potential degradation of the filter material during operation.

A couple of filter concepts have been tested successfully for breath-relevant compounds with remarkable results. Membranes based on microporous materials (e.g., zeolites) – so-called molecular sieves - are particularly attractive if confounders feature larger molecular sizes than the target analyte. This has been demonstrated recently with a zeolite MFI[132]/Al_2O_3 membrane placed upstream of a non-specific Pd-SnO_2 sensor increasing the formaldehyde selectivity to >100 over other major breath molecules including acetone, ethanol, NH_3 or isoprene[133] (Figure 3f). The membrane, however, also decreased sensor response and increased the response and recovery times for formaldehyde[133]. This concept can be extended to other analytes as a variety of zeolite frameworks are available with a wide range of separation properties[134].

Sorption filters based on packed beds of activated alumina have been used to retain hydrophilic compounds (e.g., ketones, NH_3 and alcohols) resulting in superior selectivity for hydrophobic analytes that pass unhindered[135]. This way, hydrophobic isoprene is detected selectively in simulated breath mixtures at 90% RH by a non-specific Pt-SnO_2 sensor without compromising fast response and recovery times[135]. Hydrophobic activated carbon, on the other hand, removes VOCs and is widely applied in commercial CO sensors[136]. Sorbents can be used also as pre-concentrators by operating them in a thermocyclic mode for controlled ad-/absorption and desorption, as demonstrated with Tenax TA in microfluidic chips[137]. Also gas chromatographic columns have been applied for VOC separation breath analysis[83].

Stability

Usual operating temperatures of SMOx sensors are in the range of 200 to 500 °C. An intrinsic issue of nanostructured materials is their poor thermal stability. To avoid structural alterations and thus performance deterioration during sensor operation (e.g., sensor drift or reduced sensitivity), temperatures should be lowered. However, this is typically not desirable as surface reactivity is changed compromising selectivity, sensitivity and response time. Alternatively, sensing materials can be thermally stabilized at the nanoscale. Common approaches include the addition of foreign elements as surface additives or dopants to inhibit particle and crystal growth[138] and phase transformation[139]. Such strategies are quite effective as can be demonstrated for ZnO, an often chosen but rather unstable sensing material at its pristine state. In fact, pure ZnO nanoparticles grow significantly already at room temperature in the presence of water vapor, as had been observed for crystal sizes below 20 nm[140]. Adding only 2.5 mol% of Ti as dopant largely inhibits this growth, even at elevated temperature (e.g. 500 °C for 5 h)[100].

Device integration

Portability and low cost are essential requirements for a breath detector to enter daily use. A key element is the sensor itself and its miniaturization, scale-up production and integration into a compact device are primarily engineering tasks. State-of-the-art and proven scalable microfabrication technology offers solutions to miniaturization as SMOx sensing films can be grown[141]/deposited (e.g., by doctor blading or thermophoresis from flame aerosol streams[95]) onto usually Si-wafer[142] based micromachined substrates. That way, sensor chip sizes below 1 mm^2 can be achieved.

Power consumption is a constraint of current SMOx sensors requiring heating to enhance their surface reactivity and reaction kinetics (thus rapid response and recovery times). Power consumption can be lowered by reducing thermal mass and improving thermal insulation of the sensing element[10]. Micromachined sensor substrates with a suspended heater (μ-hotplates) are especially suitable as only a tiny membrane containing the sensing film is heated locally[10]. This results in power consumption of few tens of mW at typical sensor operational temperatures of 250 – 500 °C[11], sufficiently low for battery-driven devices. Additionally, power consumption can be drastically reduced by optimizing sensor operation, e.g., applying on-demand and pulsed heating[143]. Alternatively, conductive polymers (e.g., polyaniline[144]) and carbon nanotubes[145] possess promising sensitivities already at room temperature. However, these suffer usually from slow response and recovery times impeding their application in breath analysis.

Miniaturization of the sampler is another critical task as functionality for standardized sampling (specified above) has to be ensured. When designing the sampler, mouth-to-sensor pathways should be short and without dead-volumes[12]. Disposable mouthpieces are required to preclude inter-subject contamination and droplet traps are necessary to catch saliva before entering and contaminating the sampler[79]. Also, all surfaces in contact with breath should be

made of inert materials (e.g., Teflon) and heated to avoid humidity condensation and analyte ad-/absorption[12].

Finally, simple operation of the breath detector and comprehensible visualization of results are essential for use by the laymen. Ideally, breath detectors should communicate with smartphones due to their widespread application, powerful data processing and storage capacities and high resolution displays to illustrate data and interact with the user. Also, data transmission to "clouds" seems quite attractive for combined assessment with other user information and communication with clinicians. The feeding of such personal, dense and dynamic data "clouds" is the basis of "4P" medicine[3].

Clinical applicability

Before and during translation of a laboratory-based breath sensor into clinical practice, its applicability must be proven. In specific, the measured biomarker must satisfy several criteria to be accepted. These include a proof-of-concept that its concentration differs between subject with and without illness with definable reference values[146]. Furthermore, the respective breath sensor needs to be simple-in-use for both, clinician and patient, and meet certain methodological requirements including reliability, repeatability and compliance with clinical "gold standard" tests upon application on humans[146]. Crucial part is the assessment of the device's precision and accuracy. In particular, a defined number (e.g. 95%) of measurements of the same probe must be within a defined range of obtained values (e.g. ±10% of the mean) to demonstrate sufficient precision. To fulfill a required accuracy, the results of the new medical device should not exceed a defined deviation from the "gold standard" measurements. For many tests that are used by patients in everyday life, such guidelines exist – e.g. for self-measurements of blood glucose[147].

Pilot studies in the clinical environment

So far, only few breath sensors have made it out of the laboratory and were tested on humans, though primarily in pre-clinical settings. Nevertheless, this step is crucial to evaluate their analytical performance on *real* breath. Simulating its full complexity with hundreds of compounds at concentrations spanning several orders of magnitude[2] with laboratory gas mixtures is simply impossible. Important in the design of a breath study is the involvement of a statistically significant number of volunteers and a cohort composition that reflects the actual purpose of the breath sensor. For instance, if the breath test aims to support a physician in a diagnostic decision on asthma, asthmatic patients and healthy controls should be included to cover a large range of breath compositions.

When testing humans, actual breath concentrations of the marker are unknown as every analytical instrument will have errors. The best approach to evaluate a breath sensor is an agreement analysis (e.g., Bland-Altman[148]) with a highly selective and sensitive analytical instrument. For online breath analysis, high-resolution mass spectrometers are attractive, for instance, proton transfer reaction time-of-flight mass spectrometry (PTR-TOF-MS)[149], selective ion flow tube mass spectrometry (SIFT-MS)[150] or SESI-MS[151]. When performing such tests, it is crucial to ensure that the *same* breath sample is analyzed, as ensured by state-of-the-art sampler designs for research purposes[79]. Different samples or even sampling methods between sensor and standard methods may alter breath composition and introduce errors, such as systematic biases.

For instance, breath sensors based on Si-doped WO_3 nanoparticles have been applied to monitor breath acetone (as indicator for fat burn[152]) online[153] and offline[82]. When measuring the breath acetone of 20 volunteers (270 samples) during 3 x 30 min of cycling and 3 h post-exercise rest (Figure 4a,b), the sensor nicely followed the individual breath acetone dynamics (Figure 4c), in good agreement to PTR-TOF-MS (Figure 4e, Pearson's correlation coefficient $r = 0.97$). Remarkably, the individual onset of enhanced fatty acid metabolism was correctly

recognized by this sensor with most pronounced intensities during the post-exercise rest, as confirmed by parallel blood measurements (β-hydroxybutyrate) (Figure 4d). The same sensor was applied to monitor breath acetone concentrations in 11 volunteers during a 36-h ketogenic diet[154]. Most interestingly, this sensor could detect accurately their breath acetone dynamics up to 66 ppm providing information about the individual state of ketosis, as indicated also by parallel blood β-hydroxybutyrate measurements[154]. Note that breath acetone and blood BOHB share similar origin in the hepatic mitochondria after β-oxidation of fatty acids and further biochemical transformations[25]. However, their exact relation requires further investigation. As a result, this breath sensor could be promising for application in gyms or at home to provide feedback on exercise effectiveness and/or to guide ketogenic diets.

In a next step, this sensor's accuracy and precision need to be tested in an extended cohort and compared to indirect calorimetry, the "gold standard" for estimating fat burn rates[18]. Furthermore, upcoming studies should extend the physiological but also pathological interpretation of breath acetone. For instance, obesity[155] and uncontrolled diabetes[33] are known factors to influence acetone.

Figure 4

Also polyaniline sensors have been tested successfully for breath (mouth-exhaled) ammonia detection (Figure 5a)[144]. In fact, such sensors showed good correlation with photoacoustic laser spectroscopy between 0 and 700 ppb ammonia concentrations in 11 healthy subjects (Figure 5b)[144]. In a second test, the device could clearly recognize different breath ammonia levels of 20 end-stage renal disease patients before and after hemodialysis (Figure 5c), in line with blood urea nitrogen (Figure 5d)[144]. As a result, this sensor could be attractive for hemodialysis monitoring but the robustness of mouth-exhaled ammonia as marker and the real clinical utility of such a breath test need to be clarified[52]. Even though the above mentioned cases where pilot studies, they demonstrate that selective breath sensors can work with humans despite the challenging requirements of breath analysis.

Figure 5

Clinical relevance

A sensor with an outstanding analytical performance may be clinically of little use if it does not meet certain medical requirements. First of all, the results of breath tests must fulfill a clinical need where it can support the physician and patient. In specific, it must add sufficient predictive information over established markers to improve the clinical outcome[146] (e.g., through a better diagnostic or therapeutic decision). The diagnostic accuracy of a sensor device depends on its *medical sensitivity* (i.e. ratio of correctly recognized diseased among the diseased population) and *specificity* (i.e. ratio of correctly recognized healthy among the healthy population)[156] - not to be confused with the similarly named analytical terms but with completely different meaning. Both parameters depend on the indicative power of a breath marker, the sensor performance –analytical sensitivity and specificity –and the disease *prevalence*. Furthermore, the breath test must be cost-effective.[146]

Current clinically applied breath tests target diseases/malfunctions with high prevalence in the general population (e.g., H_2 for lactose intolerance[157] or $^{13/14}C$ urea test for Helicobacter Pylori[158]). As a result, high analytical sensitivity and specificity will come along with a high medical sensitivity and specificity. However in case of diseases with very low prevalence (e.g., ovarian cancer), it is hardly possible to fulfill the required high medical sensitivity and specificity[156]. Therefore, the U.S. Food and Drug Administration has recommended against such screening tests[159]. This point of view remains often unrecognized by sensor developers but is crucial for medical applications and has been described nicely by Pendley and Linder[156]. Also, the diagnostic value of a new breath sensor is determined not only by its clinical need and diagnostic accuracy. The interpretability and consequence of the test results for both patient and medical professional must be considered as well.

Despite extensive investigations during the past decades, “unique” breath components or patterns as disease indicators have not been found with few exceptions including H_2 and CH_4 for carbohydrate intolerance[14] or NO for asthma[20]. Most breath markers are not related exclusively to a disease but affected by several biochemical pathways and physiological states. A critical clinical advantage of portable devices is the possibility of repetitive breath analysis even in everyday life. This provides the opportunity to register longitudinal concentration profiles of several breath markers for a subject. Such profiles may be of much higher diagnostic value than single measurements and may help to overcome or even exploit current limitations of breath markers (e.g. large intra- and inter-individual variations, different physiological and pathological influence vectors, contaminations, fast changes). Furthermore, by introducing methods of machine learning, continuous breath sample analysis may help to monitor the individual health status during therapeutic interventions and provide information about their effectiveness. An example is the continuous glucose monitoring system which has become widely available for the measurement of subcutaneous blood glucose concentrations in diabetics[160].

Conclusions: challenges and solutions in designing breath sensor

Detecting volatiles in exhaled human breath opens exciting opportunities for new medical diagnostic and monitoring devices. Chemoresistive sensors can enable portable, low-cost and simple-in-use breath analyzers for routine application in daily life in a wide population. During development, sensor systems (sensing material, arrays, filters) need to be designed and tested rigorously to meet the demanding requirements of breath analysis.

Most challenging seems to be the *selective* detection of targeted breath markers in the complex human breath (> 800 compounds). Particular promise lays in advances of new fabrication methods with their capacity to systematically tailor the surface reactivity of sensing nanoparticles by altering their composition, crystal phase and morphology. Further

improvements are expected through combinatorial selectivity when incorporated into orthogonal sensor arrays. Also sorption and microporous filters preceding sensors allow more flexible selectivity control by exploiting a breath markers sorption, molecular size and diffusion properties.

Finally, we would like to encourage breath sensor developers (remaining with their innovations too often in basic scientific laboratories) to evaluate their sensors in a clinical setting on humans early on. Only in tests on humans, the functionality and true value of a breath sensor can be evaluated and problems identified. Therein, correct and reproducible breath sampling is a key prerequisite. Current efforts by the breath analysis community aim to a consensus on methodologies for various breath compounds. The development of breath analysis as a clinically applicable monitoring and diagnostic tool or even as predictor of disease risks currently seems to lack systematic methodology and crystal clear proof-of-concept. So, the efforts to understand the underlying biochemical and physiological mechanisms of breath markers must be intensified. Subsequent steps, such as prospective assessment, establishment of reference values and careful analyses of their clinical applicability and relevance need to be advanced systematically.

Developing breath sensors is a complex – nevertheless exciting – task requiring strong commitment, persistence and in-depth interaction between scientists, engineers and clinicians. In light of the tremendous promise, we believe it is worth all efforts! Even if one cannot predict the future, extrapolating from the past and present rapid progress in breath sensor development, it is almost certain that sensors will play an important role in the next generation of non-invasive medical diagnostics and monitoring as part of the “4P” medicine.

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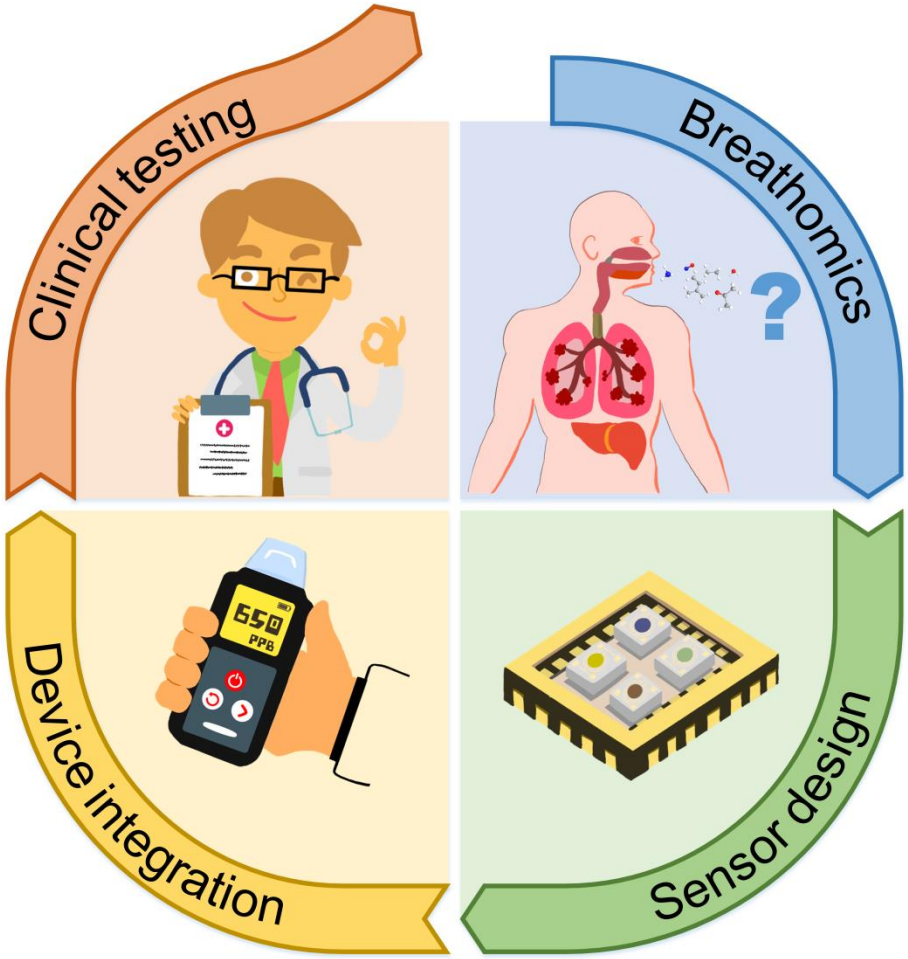
Table of Content graph



Figures & Captions

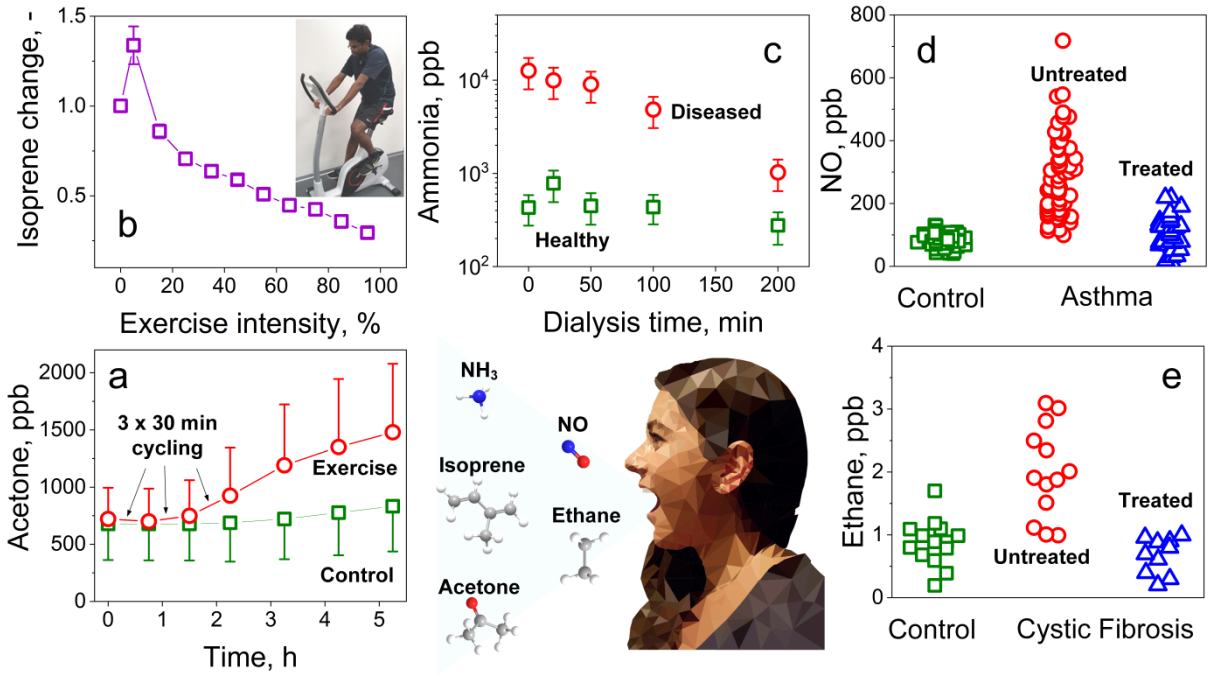


Figure 1: Selected breath markers to monitor metabolic or inflammatory conditions. (a) Acetone increases during exercise (3 x 30 min cycling at moderate intensity) and post-exercise rest (red circles) compared to controls that did not perform cycling (green squares).[36] (b) Isoprene levels show a pronounced increase at the beginning of muscle activity.[35] Inset image reprinted with permission from ref [36]. Copyright (2017) American Chemical Society.(c) Ammonia levels decrease significantly during hemodialysis in end-stage renal disease patients (red circles). Green squares indicate healthy controls.[50] (d) Untreated asthmatic patients exhibit elevated NO levels (red circles) compared to treated asthmatics (blue triangles) and healthy controls (green squares).[161] (e) Ethane is enhanced in patients suffering from cystic fibrosis (red circles) compared to treated asthmatics (blue triangles) and healthy controls (green squares).[70] Schematic of exhaling female reprinted with permission from ref [100]. Copyright (2016) The Royal Society of Chemistry.

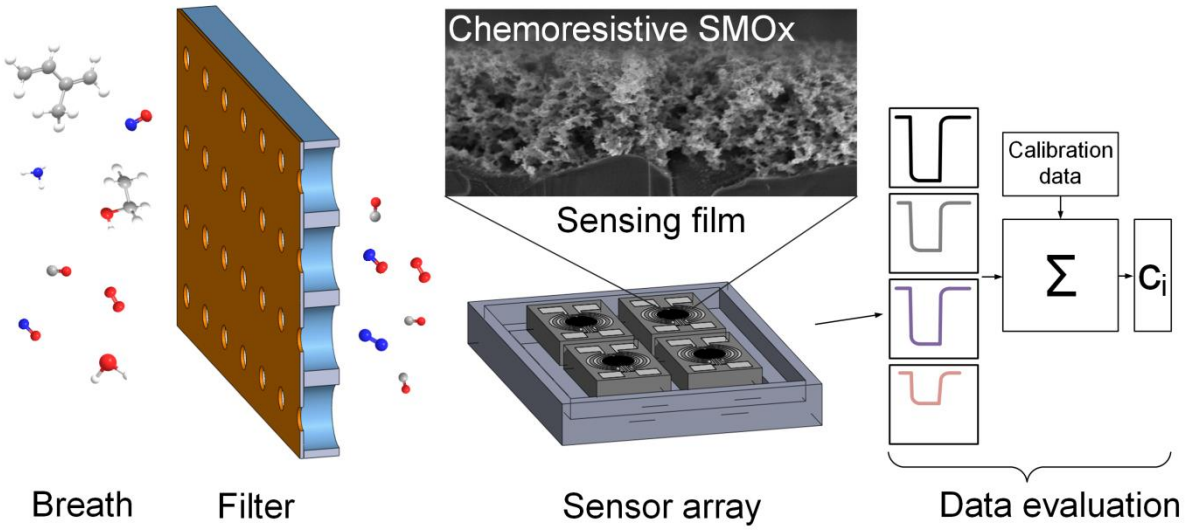


Figure 2: Components of a semiconductive metal oxide-based sensor system affecting selectivity[162]. Filter membrane reprinted with permission from ref [133]. Copyright (2018) Elsevier.

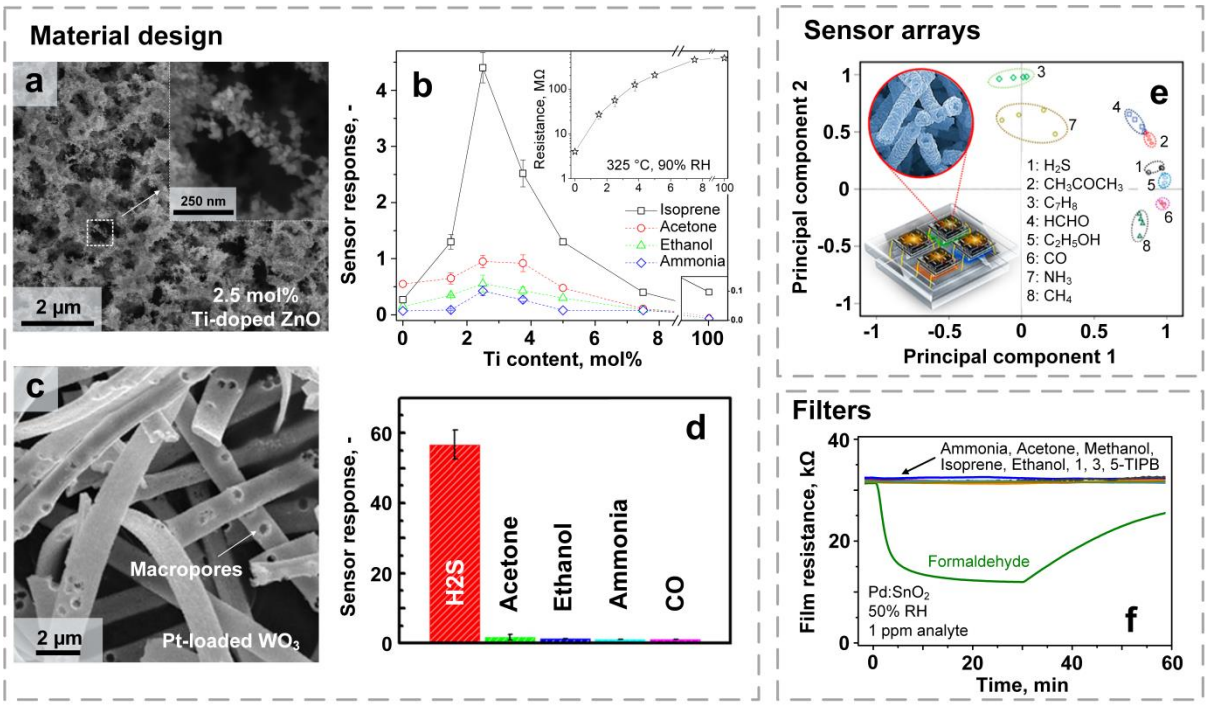


Figure 3: Tailoring selectivity: (a) Top view of a highly porous 2.5 mol% Ti-doped ZnO sensing film and (b) the corresponding sensor performance for different doping levels. (a,b) Reprinted with permission from ref [100]. Copyright (2016) The Royal Society of Chemistry. (c) Image of mesoprous Pt-loaded WO_3 and (d) the corresponding sensor performance showing high H_2S selectivity. (c,d) Reprinted with permission from ref [107]. Copyright (2018) American Chemical Society. (e) Various gas molecules are identified by principal component analysis by using a sensor array based on different WO_3-based materials. Reprinted with permission from ref [125]. Copyright (2018) American Chemical Society. (f) Only formaldehyde is detected when a microporous zeolite membrane is applied upstream of a non-specific Pd-doped SnO_2 sensor. Reprinted with permission from ref [133]. Copyright (2018) Elsevier.

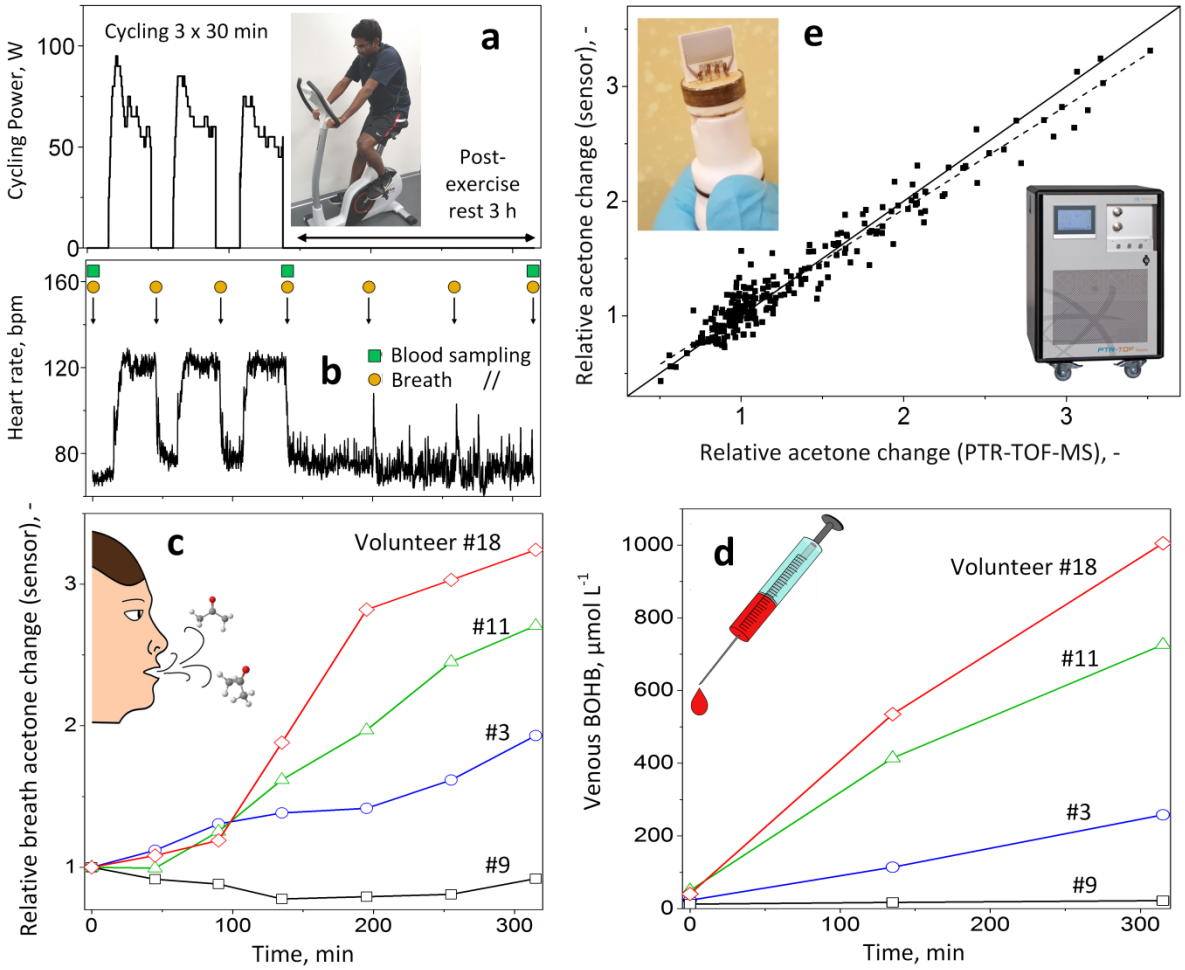


Figure 4: (a) Measured cycling power and (b) heart rate of a volunteer when performing 3 x 30 min of cycling followed by 3 h rest. Squares and circles indicate the sampling of blood and breath, respectively. (c) Relative breath acetone change and (d) blood β-hydroxybutyrate (BOHB) exemplary for four volunteers. (e) The sensor shows good correlation to acetone measurements with a state-of-the-art PTR-TOF-MS. Reprinted with permission from ref [36]. Copyright (2017) American Chemical Society.

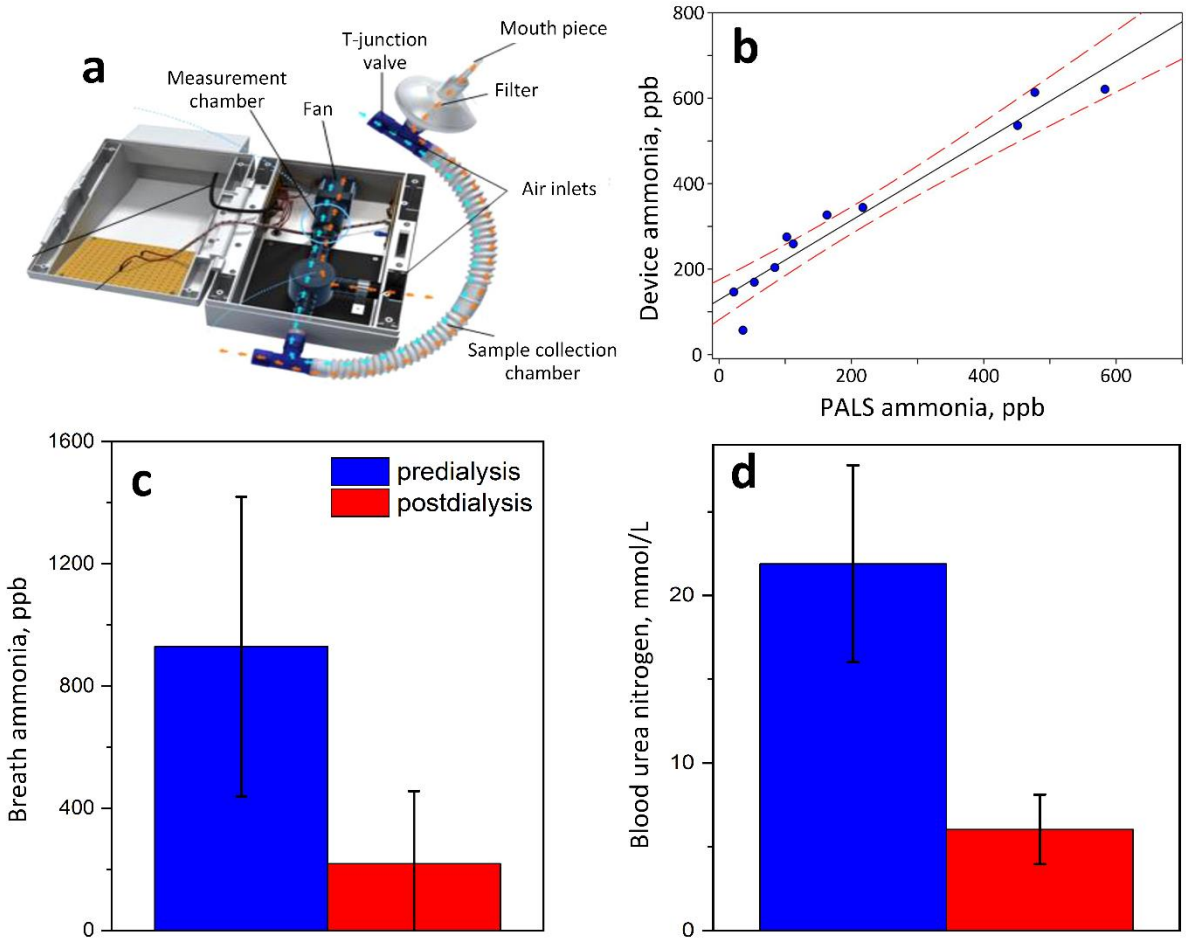


Figure 5: (a) Schematic of the breath ammonia measurement system. (b) Device comparison to photo acoustic laser spectroscopy of 11 volunteers. (c) Mean breath ammonia and (d) blood urea nitrogen before (blue) and after (red) dialysis of 20 end-stage renal disease patients. Reprinted with permission from ref [144]. Copyright (2013) American Chemical Society.