Extended Abstract of:

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Selective gas sensors from flames for breath analysis

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1. Summary:

Novel technology to monitor health parameters in a personalized, convenient and on-demand fashion can revolutionize medical diagnostics and treatment of major diseases (e.g. cancer, obesity, kidney dysfunction or diabetes). Current methods are invasive, thus hardly suitable for daily use or even continuous monitoring. Exhaled breath is rich in physiological information, easily accessible and therefore ideal for this purpose. For this, suitable breath detectors that are portable, low-cost, user-friendly and proven in clinical environments are needed. 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 mostly failing on the demanding sensitivity and selectivity requiement in breath. In fact, most markers occur at parts-per-million (ppm) to parts-per-billion (ppb) concentrations that need to be detected within the >800 compounds in exhaled breath.

In this thesis, novel sensor concepts and systems were designed to systematically address the required selectivity and sensitivity in breath analysis. Key breath markers (including ammonia, isoprene, formaldehyde and acetone) were targeted, where no reliable chemical sensors exist to date. Therefore, gas sensing materials were explored and engineered at the nanoscale by flame spray pyrolysis (FSP). Furthermore, orthogonal sensor arrays with appropriate statistical evaluation algorithms and microporous filter membranes were pioneered. The resulting gas sensor systems were tested on humans in clinical environments. The research of this thesis has led to a new generation of molecule-selective breath sensors that are promising for non-invasive medical diagnostics, monitoring and treatment in personalized medicine.

2. Addressed problem & current situation:

Despite a growing diagnostic toolset and a plethora of preventative and therapeutic interventions, a major challenge in medicine 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 “4P” medicine 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 outcomes between patients (e.g., obesity[8] or cancer[9]). For daily breath analysis in wide-spread populations, breath detectors are required that are simple-in-use and portable.

There are several techniques for breath component detection that are categorized mostly into three groups: (1) Methods based on gas chromatography or mass spectrometry, (2) laser-absorption spectroscopic techniques and (3) chemical sensors. With the most common gas chromatography (GC)[10], various detection methods can be coupled to identify breath components, such as mass spectrometry (MS)[11], flame ionization detector (FID)[12] and ion mobility spectrometry (IMS)[13]. However, pretreatment of the breath is necessary to concentrate the trace analyte by solid sorbent materials and to remove water vapor that can damage the GC column[14]. Both steps induce undesirable loss of organic compounds in the breath sample[15]. In the last decades, more sophisticated methods were developed for real-time quantification of several trace gases in both air and breath such as quadrupole time-of-flight mass spectrometry (QTOF-MS)[16,17], proton transfer reaction mass spectrometry (PTR-MS)[18] and selected ion flow tube mass spectrometry (SIFT-MS)[19]. Even though high selectivity, sufficient sensitivity and low limit of detection (LOD) have been achieved with GC- and MS-based techniques, high investment costs, bulky instrumentation and the need for well-trained operators limit their application as portable and easily applicable breath detector.

Chemical sensors could overcome this due to their compact design[20], low cost and power consumption[21] being ideal for integration into handheld devices[22]. Having such inexpensive technology creates also new opportunities for healthcare in low-income countries with scarce medical resources[23]. 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.

3. Implementation:

In this thesis, novel high-performance gas sensing materials based on chemoresistive metal-oxides were explored by flame spray pyrolysis (FSP). As a versatile and scalable method[24], it allows the fabrication of metal-oxides, metal salts with controlled composition and morphology (e.g. crystal/particle size[25]) at high purity. Selectivity to the target analytes was obtained by forming solid solutions, surface decoration with foreign oxides & noble metals[26]. Gas sensing films were directly deposited by thermophoresis[27] onto micromachined Si wafer-based substrates with integrated electrical circuitry (Figure 1)[28]. During deposition, the nanoparticles aggregate and agglomerate to form highly porous networks [27] that can be monitored by insitu film resistance read-out[29]. Such highly porous film morphologies are favorable for gas sensing due to their open, thus easily accessible, structure and large specific surface area to detect even lowest ppb concentrations with response times of seconds to few minutes[28], required for breath analysis.

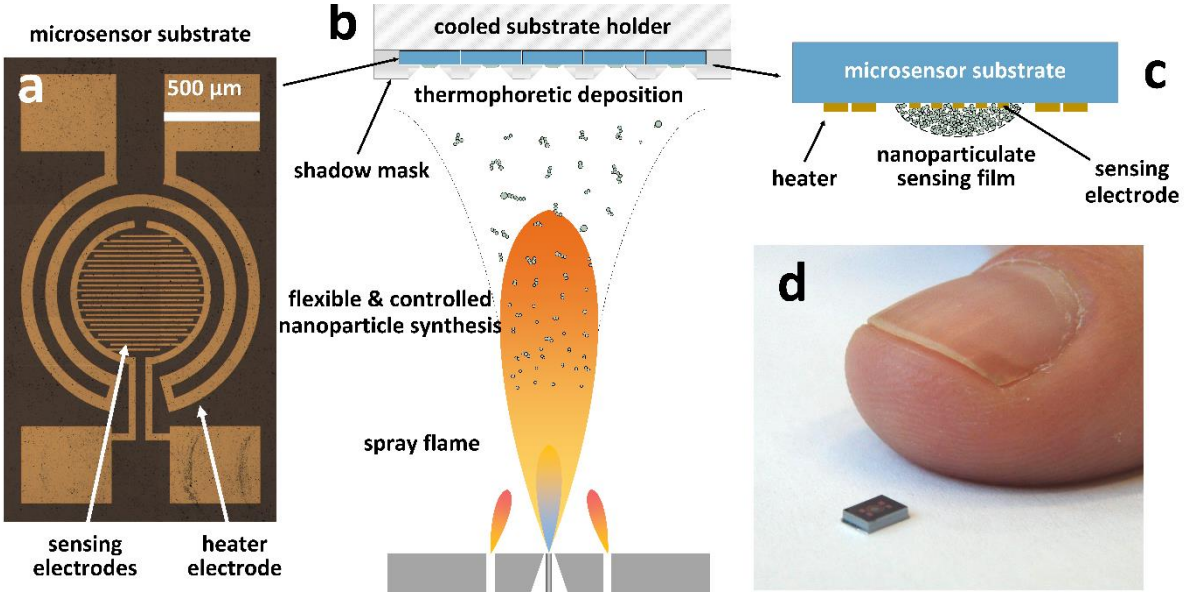

***Figure 1**: Process schematic: (a) microsensor substrate features a circular-shaped sensing area with a set of interdigitated Pt electrodes. (b,c) Flame-made sensing particles are accurately deposited by thermophoresis on such substrates using a shadow mask. (d) Such sensors are rather small in comparison, for instance, to the index finger. Figure adapted from [28].*

In a first step, ammonia-selective Si-doped α-MoO_3 gas sensor were fabricated[30]. Ammonia is an important breath marker for non-invasive detection of kidney dysfunction and monitoring of hemodialysis[31]. A key novelty is the thermal stabilization of α-MoO_3 by Si-doping inhibiting sintering and crystal growth at the operational conditions of such sensors. Therefore, pure and Si-doped MoO_x nanoparticles were made by FSP and directly deposited onto sensor substrates forming highly porous films with ribbon-like (Figure 2a) and nanoparticle/ needle-like (Figure 2b) morphologies, respectively. *In-situ* XRD analysis of the MoO_x phase dynamics revealed a thermally-induced recrystallization of β-MoO_3 at 300 - 350 °C and optimal annealing at 450 °C for synthesis of highly nanocrystalline α-MoO_3.

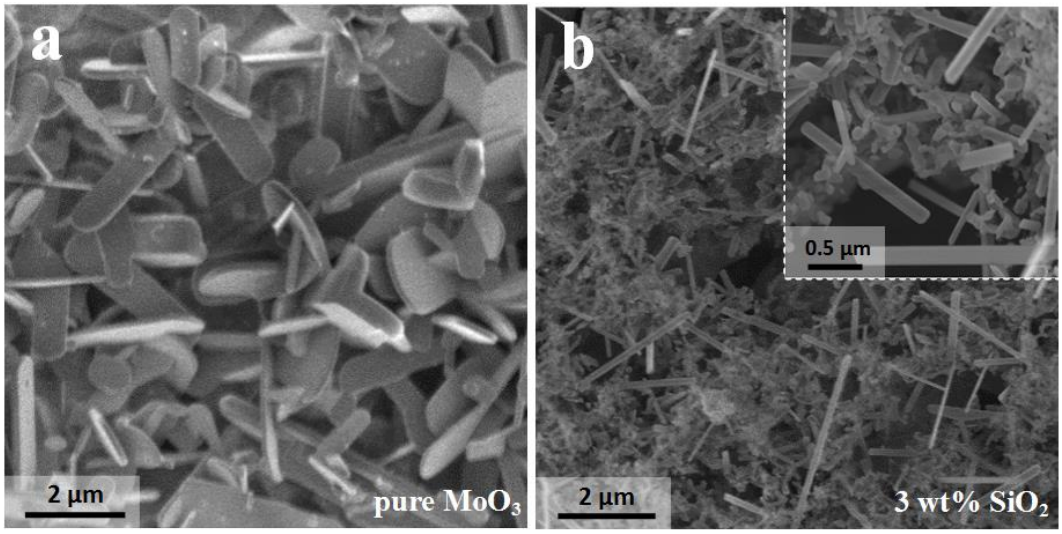

***Figure 2:** SEM image (top view) of (a) pure and (b) 3 wt% Si-doped MoO_3 films after annealing at 450 °C for 5 h. (a) Pure MoO_3 has grown to thin belts (platelets, ribbons or disks) with dimensions of several µm. (b) The Si-doping alters drastically that morphology to increased porosity by a finer network consisting of agglomerated nanoparticles and needle-like structures (inset). Adopted from [30].*

For selective ammonia sensing, the optimum SiO_2 content was 3 wt% and the operational temperature 400 °C (Figure 3a). This sensor showed superior ammonia selectivity towards acetone, NO and CO, and accurately detected breath-relevant ammonia concentrations down to 400 ppb under 90% relative humidity (RH) (Figure 3b). As a result, a stable and inexpensive sensor for ammonia is presented which has the potential for further development towards a hand-held device for the early-stage diagnosis and monitoring of kidney dysfunction.

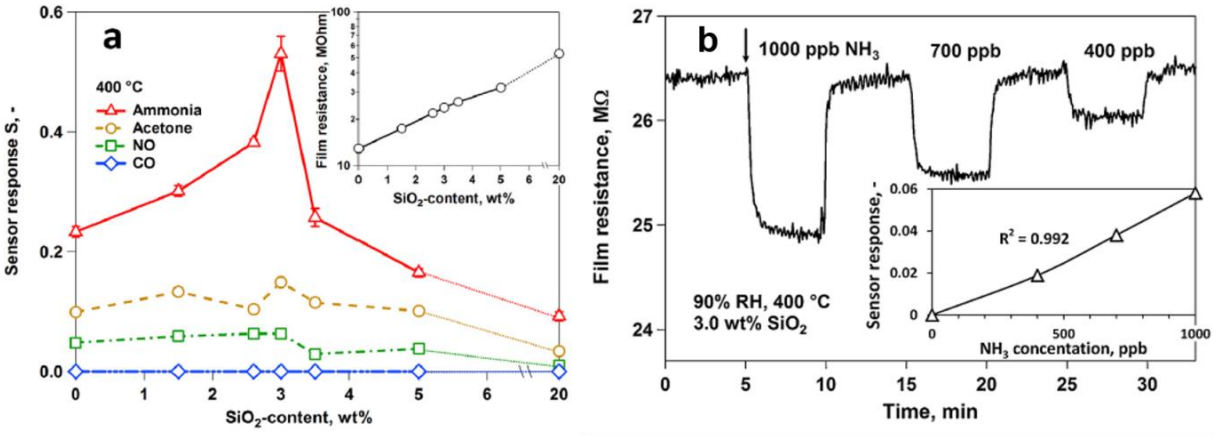

Figure 3: *(a) Sensor response as a function of SiO_2-content to 1 ppm ammonia (triangles), acetone (circles), NO (squares), and CO (diamonds) in dry air at 400 °C. All sensors show high sensitivity to ammonia. An optimal Si-dopant level with respect to sensitivity and selectivity is identified at 3.0 wt%. (b) The film resistance of the optimally Si-doped (3 wt% SiO_2) MoO_3 sensor upon exposure to 1000, 700, and 400 ppb of ammonia at 90% RH and 400 °C. The corresponding calibration (inset) is nearly linear. Adopted from [30].*

Next, the first *isoprene-selective* sensors (to our knowledge) was designed.[32] Exhaled isoprene could enable non-invasive monitoring of cholesterol-lowering therapies[33]. The sensor is made of nanostructured, chemoresistive Ti-doped ZnO particles (10 - 20 nm crystal size) produced by FSP and directly deposited in *one step* onto compact sensor substrates forming highly porous films (Figure 4a). The constituent particles consist of stable Ti-doped ZnO solid solutions for Ti levels up to 10 mol% apparently by substitutional incorporation of Ti^{4+} into the ZnO wurtzite lattice and dominant presence at the particle surface.

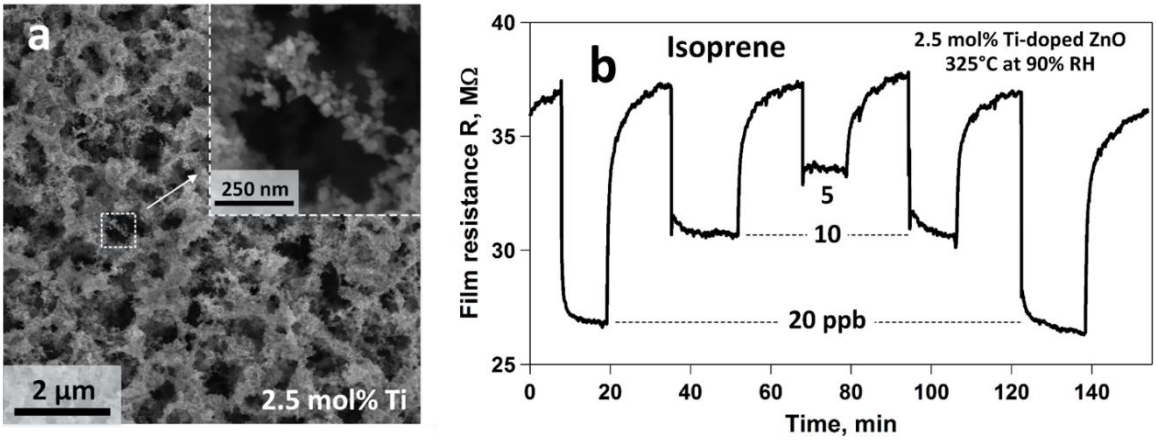

Figure 4: *(a) Scanning electron microscopy image (top view) of a 2.5 mol% Ti-doped ZnO film after annealing at 500 °C for 5 h. (b) Film resistance of an optimally doped Ti-doped ZnO (2.5 mol%) sensor upon exposure to 5, 10 and 20 ppb of isoprene at 325 °C and 90% RH. Adopted from [30].*

These Ti^{4+} point defects strongly enhanced the isoprene sensitivity (*> 15 times* higher than pure ZnO) and turn ZnO *isoprene-selective*, while also improving its thermal stability. *In-situ* infrared spectroscopy confirms that Ti^{4+} intensifies the surface interaction of Ti-doped ZnO with isoprene by providing additional sites for chemisorbed hydroxyl species. In fact, at an optimal Ti content of 2.5 mol%, this sensor shows superior isoprene responses compared to acetone, ammonia and ethanol at 90% RH. Most notably, breath-relevant isoprene concentrations can be detected accurately *down to 5 ppb* with high (> 10) signal-to-noise ratio (Figure 4b). As a result, an inexpensive isoprene detector has been developed that could be easily incorporated into a portable breath analyzer[22] for non-invasive monitoring of metabolic disorders (e.g. cholesterol).

Formaldehyde is a potential breath marker for lung cancer[34] and a tracer for indoor air quality monitoring[35]. Its typical concentrations are below 100 ppb posing a sensitivity and selectivity challenge to current portable sensor systems. Here, we present a highly sensitive, selective and compact sensor array for real-time quantification of formaldehyde at realistic conditions.[28] This array consists of four nanostructured and highly porous Pt-, Si-, Pd- and Ti-doped SnO_2 sensing films directly deposited onto silicon wafer-based microsubstrates by FSP (Figure 5a). The constituent sensors offer stable responses (24 h tested) and detection of formaldehyde down to 3 ppb (signal-to-noise ratio > 25) at breath-realistic 90% relative humidity. Each dopant induces different analyte selectivity enabling *selective* detection of formaldehyde in 2-, 3- and 4-analyte mixtures by multivariate linear regression. In simulated breath, formaldehyde is detected with an average error ≤ 9 ppb (Figure 5b) using the present array and overcoming selectivity issues of single sensors. This device could facilitate easy screening of lung cancer patients. Recently, this approach has been extended to *orthogonal* sensor arrays[36] that have been tested successfully to monitor low-ppb concentrations of human breath- and skin-emitted volatiles for search and rescue[37].

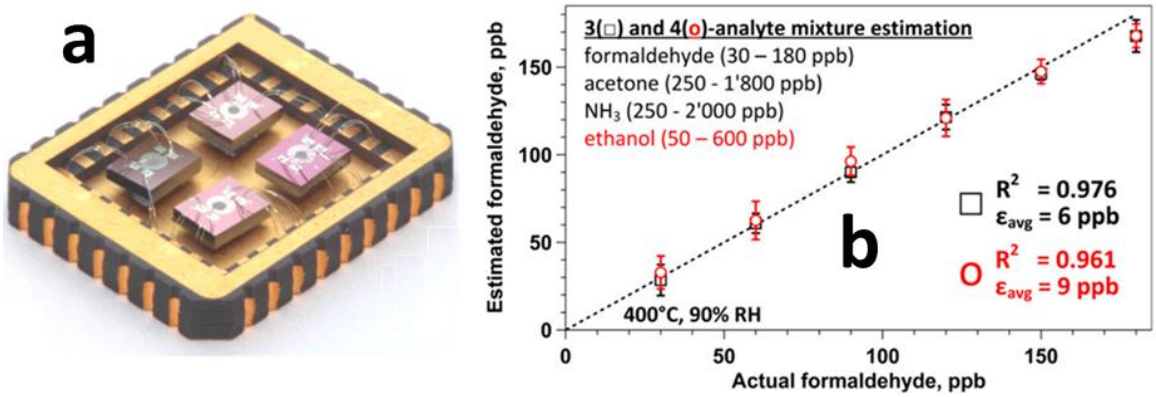

Figure 5: *a) Sensor array combining Pd-, Pt-, Si- and Ti-doped SnO_2 sensors . b) Array estimation of formaldehyde at 90% RH in breath-relevant three- (squares) and four-analyte (circles) mixtures.[38]*

Also filters can enhance the selectivity of gas sensors. Here, the use of microporous membranes to enhance the selectivity of gas sensors was pioneered[39]. Highly selective *zeolite membranes* were applied to pre-separate gas mixtures. Zeolites - broadly applied in catalysis and gas separation -

effectively separate molecules based on kinetic diameter, sorption and diffusion characteristics[40]. Therefore, zeolite membranes are suitable filters for gas sensors removing undesired species from mixtures like exhaled breath. As proof-of-concept, a zeolite MFI/Al_2O_3 membrane is placed upstream a highly sensitive but weakly selective Pd-doped SnO_2 sensor (Figure 6).

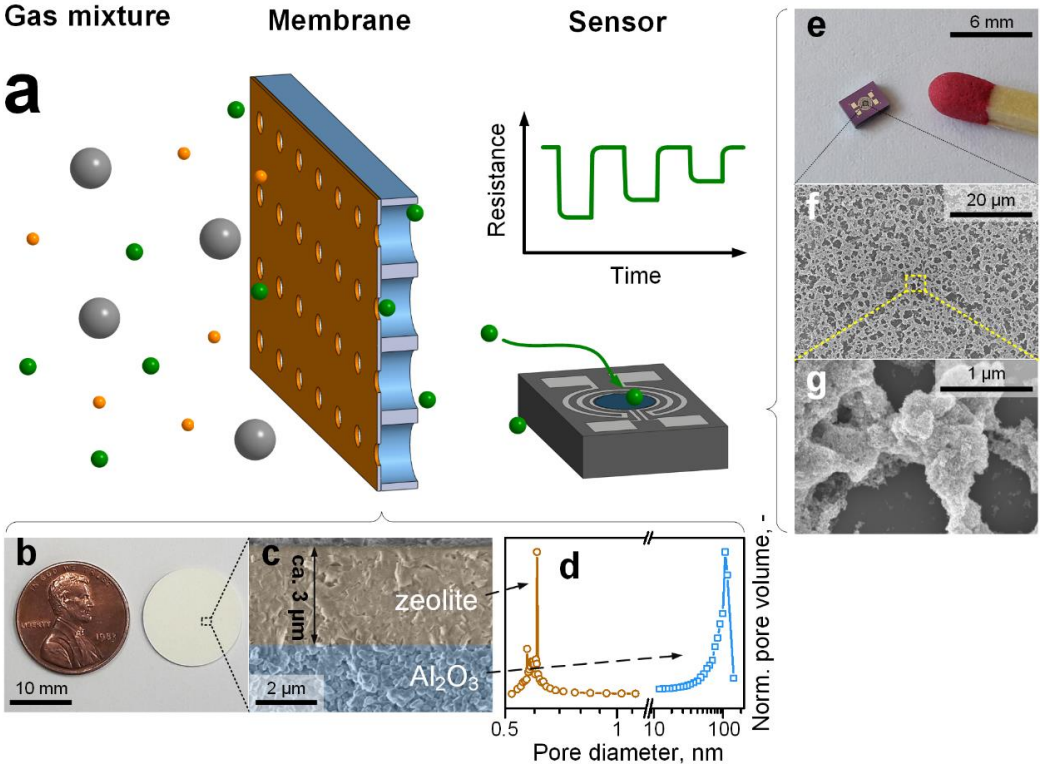

Figure 6: *(a) Concept of the membrane-sensor assembly for selective analyte detection. (b) Image of the coin-type membrane that consists of a dense and microporous zeolite layer (brown-shaded) supported on porous Al_2O_3 (blue-shaded), as indicated by cross-sectional SEM (c). (d) Zeolite (brown) forms pores predominantly with diameters of 0.57 and 0.61 nm while the Al_2O_3 supports features pores >40 nm . (e) Image of the compact sensor that features a sensing film, as shown by top-view scanning electron microscopy (f,g). Adopted from [39].*

Their combination exhibits exceptional selectivity (*>100*) for formaldehyde down to *30 ppb* at 90% relative humidity (Figure 7), outperforming state-of-the-art detectors by more than an order of magnitude. This novel concept is readily extendable to other tracers, as manifold combinations of *widely tunable* microporous membranes[40] and gas sensor types exist. This could enable a new class of highly sensitive and selective portable breath detectors or compact indoor air quality monitors.

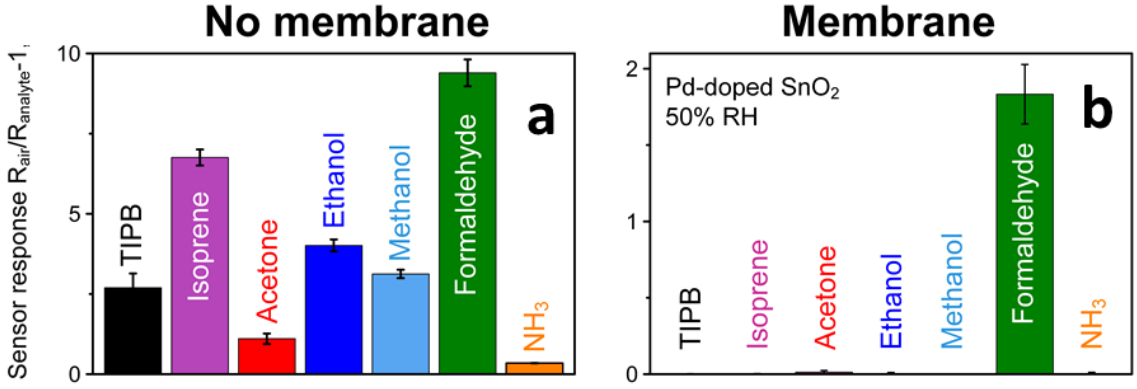

Figure 7: *Pd-doped SnO_2 sensor response without (a) and with (b) membrane to 1 ppm of ammonia (orange), acetone (red), methanol (light blue), TIPB (black), ethanol (blue), isoprene (purple) and formaldehyde (green). Adopted from [39].*

Finally, such flame-made breath sensors were tested on humans in a clinical setting. Therefore, *acetone-selective* Si-doped WO_3 sensors were combined with a tailor-made end-tidal breath sampler[41] to follow body fat burn rates in *real-time*[42] (Figure 8). Acetone is a byproduct of the fatty acid metabolism in the hepatic mitochondria[43]. We tested this sensor on 20 volunteers during exercise and rest and measured their *individual* breath acetone concentrations in good agreement to bench-top mass spectrometry (PTR-TOF-MS, Pearson's correlation coefficient 0.97).

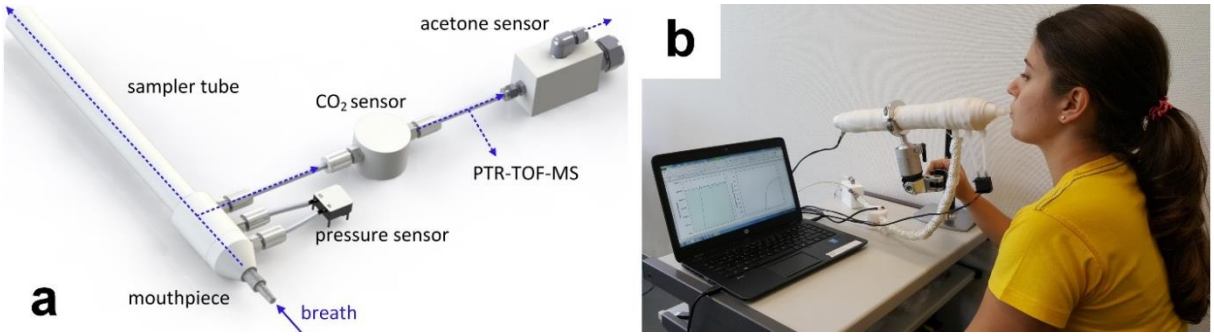

Figure 81: *a) Illustration of the breath analyzer that combines the acetone sensor with a sampler to extract breath in a standardized and monitored fashion. b) Breath analyzer in operation: the subject exhales into the sampler tube while receiving visual feed-back on airway pressure and duration to reach and maintain desired values. The acetone sensor is providing immediate analysis results.*

During exercise (Figure 9a,b), this sensor reveals clearly the onset and progression of increasing breath acetone levels that indicate intensified body fat metabolism (Figure 8c), as validated by parallel venous blood β-hydroxybutyrate (BOHB) measurements (Figure 8d). Most important, we found that the body fat metabolism was especially pronounced for most volunteers during fasting for 3 h after exercise. As a result, this simple breath acetone sensor enables easily applicable and hand-held body fat burn monitoring for *personalized* and *immediate* feed-back on workout effectiveness that can guide ketogenic dieting[44] as well.

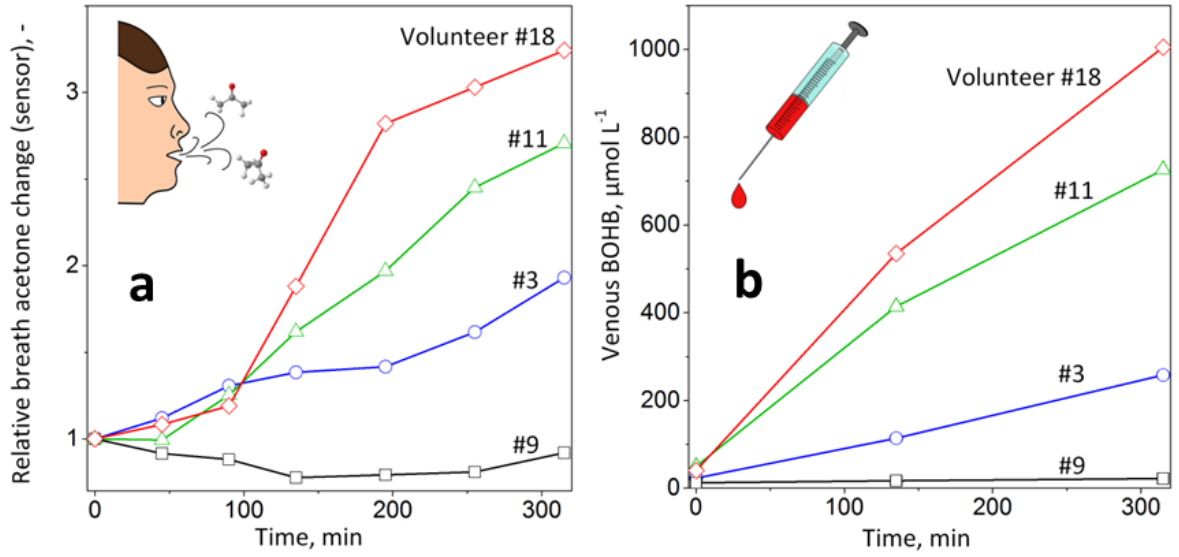

Figure 9: *Body fat burn monitoring during exercise and rest: (a) Individual breath acetone changes (relative to initial value) measured by the sensor of representative subjects undergoing the testing course with 3 x 30 min cycling on an ergometer to stimulate the body fat metabolism and 3 h post-exercise rest. (b) Corresponding blood BOHB concentrations that were sampled only 3 times instead of 7 as with breath (a) to minimize the discomfort for the volunteers.*

4. Relevance & Impact

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 to monitor health parameters in a wide population. This thesis has demonstrated, that nanostructured sensing materials, arrays, filters can be designed systematically and tested rigorously to meet the challenging requirements of breath analysis. This has led to a new generation of highly sensitive and selective breath sensors (for acetone, isoprene, ammonia and formaldehyde) and a framework that can be exploited for other breath compounds. Finally, tests on humans have demonstrated that such sensor work well with real breath and can be incorporated into portable devices.

This PhD thesis and directly connected follow-up research (since 2017) have led to 4 patents, 15 original research articles and one invited Perspective in *ACS Sensors* that have been highlighted extensively by the American Chemical Society, Yale Scientific Magazine, ETH News (1,2), Tagesanzeiger and Sonntagszeitung among 100+ other international news outlets since 2016. Furthermore, it has received an ETH Medal for outstanding PhD Thesis from the ETH Zürich, a Best Poster Prize for *Synthesis and Structuring of Functional Nanoparticles* and the *Royal Society of Chemistry* Poster Prize on the European Aerosol Conference (2017) as well as a nomination for the Best Poster Award on Fall Meeting of the Material Research Society (2015). Most importantly, this research has led to the creation of a start-up company (Sentiras GmbH) that aims to commercialize these breath sensors.

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