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Highly Selective and Rapid Breath Isoprene Sensing Enabled by Activated Alumina Filter

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Abstract

Isoprene is a versatile breath marker for non-invasive monitoring of high blood cholesterol levels as well as for influenza, end-stage renal disease, muscle activity, lung cancer and liver disease with advanced fibrosis. Its *selective* detection in complex human breath by portable devices (e.g. metal-oxide gas sensors), however, is still challenging. Here, we present a new filter concept based on activated alumina powder enabling fast and highly selective detection of isoprene at the ppb level and high humidity. The filter contains high surface area adsorbents that retain hydrophilic compounds (e.g. ketones, alcohols, ammonia) representing major interferants in breath while hydrophobic isoprene is not affected. As a proof-of-concept, filters of commercial activated alumina powder are combined with highly sensitive but rather non-specific, nanostructured Pt-doped SnO₂ sensors. This results in fast (10 s) measurement of isoprene down to 5 ppb at 90% relative humidity with outstanding selectivity (>100) to breath-relevant acetone, ammonia, ethanol and methanol, superior to state-of-the-art isoprene sensors. Most importantly, when exposed continuously to simulated breath mixtures (four analytes) for eight days, this filter–sensor system showed stable performance. It can be incorporated readily into a portable breath isoprene analyzer promising for simple-in-use blood cholesterol monitoring or other patho/physiological conditions.

Keywords:

isoprene, cholesterol, activated alumina, filter, adsorption, breath analysis, SnO₂, flame spray pyrolysis

Cardiovascular diseases are the leading cause of death,¹ accounting for more than 30% of global deaths in 2015.² Most of them could be preventable by reducing the major risk factors, including smoking, high blood pressure and high blood cholesterol.³ Currently, cholesterol is measured from a lipid profile obtained by a blood test. This means 9–12 hours of fasting before going to a physician for the measurement,⁴ which is both painful and elaborate, especially as often follow-up analyses are necessary due to large day-to-day variation in blood cholesterol concentrations.⁵ What is thus needed, is a fast and non-invasive method to reliably and routinely monitor blood cholesterol levels at home.

Breath analysis is a non-invasive diagnostic and monitoring technique that relies on detection of certain breath markers indicative of pathologic states.⁶ Exhaled isoprene is a by-product of the cholesterol biosynthetic pathway⁷ with typical breath concentrations ranging from 22 to 234 parts-per-billion (ppb)⁸ but even lower levels can occur in children⁹ and young adults.¹⁰ Most interestingly, a strong correlation between breath isoprene and blood cholesterol was shown for patients undergoing treatment with cholesterol-lowering lova-¹¹ and atorvastatins.¹² Increased breath isoprene levels occur also in patients with influenza,¹³ end-stage renal disease¹⁴ and after muscle activity,¹⁵ while such levels are decreased for lung cancer¹⁶ and liver disease with advanced fibrosis.¹⁷ Currently, breath isoprene is detected by mass spectrometry-(MS)¹¹ or gas chromatography-(GC)¹⁸ that are rather expensive, of limited portability and require scientific personnel to operate. Chemiluminescence measurement of isoprene is also possible but shows high interference from sulfur gases and other lower olefins, making precise measurement inaccurate.¹⁹ As a result, available methods are hardly suitable for routine breath tests.

Isoprene ($\text{CH}_2=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$) is a reactive, aliphatic hydrocarbon²⁰ that can be detected at low ppb concentrations also by nanostructured semiconductive metal-oxide (MOx) gas sensors. In specific, sensing films of Ti-doped ZnO deposited by flame aerosol

technology were shown to detect isoprene levels down to 5 ppb at breath-relevant 90% relative humidity.²¹ Such sensors are attractive for breath analysis by being inexpensive, simple-in-use and readily miniaturized²² and integrated into portable devices.²³ They also have been applied already quite successfully for non-invasive fat burn monitoring during exercise and rest.²⁴ MOx sensors, however, typically lack selectivity to detect target analytes in breath (>800 compounds)²⁵. Sufficient selectivity was obtained by material design only in few cases, for instance for acetone by ϵ -WO₃,²⁶ ammonia by α -MoO₃²⁷ or triethylamine by hollow SnO₂ microfibers.²⁸ In particular for isoprene, Ti-doped ZnO²¹ features selectivities in the range of 4 to 15 for breath-relevant acetone, ethanol and ammonia, however, it needs to be improved considering that these interferants are much more concentrated in the breath than isoprene. The major challenge in sensor material design with isoprene is the absence of distinct functional groups (hydroxyl, carbonyl, etc.) that can be exploited for selective sensor interaction.

Further molecular properties such as hydrophilicity and size can be exploited by filters to optimize sensing performance *beyond* chemoresistive surface reactivity. This concept has been applied for selective CO sensing²⁹ through adsorption of hydrocarbon interferants on activated carbon filters and for selective formaldehyde detection using size-selective microporous zeolite membranes.³⁰ Also complex GC columns have been used in combination with sensors for selective detection of trichloroethylene,³¹ alcohols,³² aromatic vapors³³ or even for multiple compounds in breath.³⁴ Such GC–sensor systems, however, require complex instrumentation (i.e. GC column, pre-concentration, ramped heating) and feature typically sluggish response and recovery times (e.g. 60 min³³ for sampling and analysis of aromatic volatiles). Consequently, they seem hardly suitable for real-time portable breath isoprene detectors.

Here, we present a novel filter–sensor concept for rapid and highly selective isoprene detection in complex breath mixtures at high relative humidity exploiting the hydrophobic nature of isoprene (Figure 1a). It consists of a packed bed of activated alumina featuring high porosity and surface area ($\sim 155 \text{ m}^2/\text{g}$)³⁵ to adsorb and retain hydrophilic breath compounds while isoprene passes unhindered (Figure 1b). Placed upstream of a highly sensitive but non-specific, nanostructured Pt-doped SnO_2 sensor, this filter is characterized for isoprene in gas mixtures with up to four components at 90% relative humidity (RH). Finally, filter regeneration and long-term stability are evaluated for eight days of continuous operation.

Experimental

Sensor fabrication

Sensing films of Pt-doped (0.15 mol%) SnO_2 are prepared by flame spray pyrolysis (FSP) and directly deposited onto sensor substrates.³⁶ For the FSP precursor solution, tin (II) ethylhexanoate (Strem, $\sim 90\%$ in 2-ethylhexanoic acid) and platinum acetylacetonate (Alfa Aesar, min. 48.0 % Pt) are dissolved in xylene (Aldrich, $\geq 99.7\%$) to give a total metal concentration of 0.5 mol/L with a Pt-doping content of 0.15 mol%.³⁷ The precursor is fed through a FSP nozzle with 5 mL/min and dispersed with 5 L/min oxygen at a pressure drop of 1.5 bar. This spray is ignited by a premixed, ring-shaped methane/oxygen (1.25/3.2 L/min) flame³⁸ while additional 5 L/min of oxygen is supplied as sheath gas. Deposition takes place by thermophoresis³⁶ of Pt-doped SnO_2 nanoparticles onto sensor substrates mounted on a water-cooled holder at 20 cm height above the burner (HAB) for 2 min. The applied Al_2O_3 substrates (15 mm $\times$ 13 mm $\times$ 0.8 mm, Electronic Design Center, Case Western Reserve University) feature interdigitated Pt electrodes (sputtered, 350 μm width and spacing) and a Pt heater on the back. To improve adhesion and cohesion of these FSP-deposited nanoparticle films, they are in-situ annealed³⁹ with a particle-free flame. For this, the substrate is lowered to a HAB of 14.5 cm and annealed for 30 s by a xylene flame (11 ml/min xylene dispersed by

5 L/min oxygen at 1.5 bar) with the same methane/oxygen flame and sheath gas as for the sensing film deposition. Prior to testing, sensors are thermally stabilized by heating in an oven (Carbolite GmbH) at 500 °C for 5 h.

Filter fabrication

The filter consists of a packed bed of 1 g activated alumina (Sigma-Aldrich, neutral pH when in water, 50-300 mesh, 155 m²/g) inside a Teflon tube (10 cm length, 15 mm inner diameter) and is firmly secured downstream by a porous, inert Teflon frit and upstream by an inert glass wool plug (Figure 2a). On both ends of the Teflon tube, tapered Swagelok connectors expand and contract the gas flow homogeneously to ensure utilization of the entire filter cross section and avoid stagnant zones. Freshly prepared filters are flushed with 1 L/min air at 90 % RH for at least 12 h to saturate the alumina surface with humidity and guarantee equilibrium conditions.

Gas evaluation

The filter–sensor system (Figure 2b) consists of the gas delivery,²⁷ activated alumina filter and Pt-doped SnO₂ sensor. The sensor is mounted on a Macor holder and installed inside a Teflon sensor chamber⁴⁰ where it is heated to 400 °C by DC current (R&S HMC8043, Germany) by the substrate back-heater. The temperature is maintained by utilizing the Pt heater as resistance temperature detector (RTD), monitored with a multimeter (Keithley, 2700, USA). The ohmic resistance of the sensing film between the interdigitated electrodes is measured by the same multimeter. Sensor responses are evaluated as:

$$S = \frac{R_{Air}}{R_{Analyte}} - 1$$

where R_{Air} and $R_{Analyte}$ denote the sensor film resistances measured in synthetic air without and with a given analyte concentration, respectively. The sensor response (t_{90}) and filter

breakthrough time (t_5) for an analyte are defined as the time to reach 90% and 5%⁴¹ of the steady-state response, respectively.

Sensor measurements were performed at a total gas flow rate of 1 L/min and 90% RH. Gas mixtures were prepared by first admixing the analyte gas standards with dry synthetic air (PanGas, hydrocarbon-free grade) by calibrated mass flow controllers (Bronkhorst, Netherlands). Analyte gases are supplied from calibrated gas standards (PanGas) in synthetic air at concentrations of 10 ppm for acetone, isoprene, ammonia and 50 ppm for ethanol, methanol, ammonia. These analytes are present in breath at relatively high concentration and are selected because of their known interaction with Pt-doped SnO₂ sensors, unlike other breath compounds like H₂⁴². The humidity level was set by guiding synthetic air through a water bubbler and dosing it to the gas mixture stream to obtain the desired relative humidity level as verified by a humidity sensor (SHT2x, Sensirion AG). Teflon gas lines were heated to ~50 °C to avoid condensation and adsorption.²⁷

Results and Discussion

Filter effect on isoprene selectivity

Figure 3a shows the sensor response profiles of Pt-doped SnO₂ to 500 ppb of isoprene (blue), acetone (red), ethanol (orange), methanol (green) and ammonia (purple) at breath-relevant⁴³ 90% RH. These analytes represent major components in exhaled breath with median concentrations higher than the 106 ppb⁴⁴ of isoprene (e.g. ammonia 833 ppb⁴⁵). The sensor detects *all* these analytes within a few seconds (e.g. $t_{90} = 2.9$ s for isoprene), sufficiently fast for real-time breath analysis. However, it *cannot* distinguish them. In fact, when evaluating the individual responses after 30 s (Figure 3b), representing a typical breath test duration,²⁴ the rather non-specific nature of Pt-doped SnO₂ becomes evident, in line with previous results.³⁷ Consequently, this sensor cannot measure isoprene selectively in breath mixtures.

Most importantly, when adding the activated alumina filter (Figure 3c), an *identical* response for isoprene is obtained with barely affected response dynamics (t_{90} of 4.2 s), while all hydrophilic analytes are held back. This results in *unprecedented* high isoprene-selectivity (>100) to all analytes (Figure 3d). Only after 40 s, the sensor starts to detect acetone while it takes even longer for the other hydrophilic analytes (full responses in Figure S-1). In specific, breakthrough times t_5 strongly vary between the analytes from 50 to 300 s for acetone to ammonia, respectively (Figure 3d in parenthesis). Important also, after analyte exposure is stopped, the sensor fully recovers the initial baseline enabling repeated measurements. Note that the breakthrough and regeneration times of hydrophilic analytes can be controlled by the activated alumina filter loading, while the response time of isoprene is barely affected (shown in Figure S-2). One gram of activated alumina was selected for deeper investigation to guarantee an interferent-free detection of isoprene, fast filter regeneration for repeated measurements and a low pressure drop of ~ 20 mbar, sufficiently small²⁴ for breath analyzers.

The selectivities achieved by the proposed filter–sensor system clearly outperform state-of-the-art chemoresistive isoprene sensors. Highest isoprene selectivities obtained so far were in the range of 4 to 15 for acetone, ethanol and ammonia with Ti-doped ZnO.²¹ Other chemoresistive sensors of TiO₂⁴⁶ and *h*-WO₃⁴⁷ could detect isoprene but did not achieve selectivities >4 . Only the chemiluminescence detector Fast Isoprene Sensor (FIS, Hills-Scientific) features similarly high isoprene selectivities, but this device is hardly suitable for routine measurements by a widespread population due to its high cost (base module \$42'000), weight (18 kg) and requirement of an external ozonizer.⁴⁸

Separation mechanism

When passing through the filter, hydrophilic analytes (i.e. alcohols, ketones, ammonia) are retained by adsorption on the activated alumina (Figure 1b) featuring extremely large surface area ($155\text{ m}^2/\text{g}$).³⁵ Note that the alumina surface should be mostly covered by bound water⁴⁹

at 90% RH because of its high affinity,⁵⁰ so gas ad-/absorption may occur on/in that layer as well.⁵¹ As a result, the strength of analyte-filter interaction should be governed by the ability for hydrogen bonding,⁵² with ammonia having four, ethanol and methanol three, acetone only two and isoprene zero hydrogen bonding sites (oxygen/nitrogen lone electron pairs & hydrogen atoms). This matches well with the t_5 of the analytes, following *the same* order (Figure 3d). Note that any water layer formed by RH (i.e. surface hydration) weakens sorption of hydrophilic compounds, as indicated by shorter t_5 for acetone at 50% RH (Figure S-3) and consistent with literature.⁵³

In contrast, isoprene is hydrophobic and passes through the filter unscathed, consistent with the sensing results (compare Figure 3a to c). Isoprene is the major hydrocarbon in breath (up to 70% of total)⁵⁴ but also other hydrophobic species (e.g. ethane, pentane)⁵⁵ should pass the filter unaffected and cause measurement errors, if interfering with the sensor. However, this can be prevented by combining this modular filter with an additional size-selective zeolite membrane to remove larger hydrocarbons (as applied already for sensing of formaldehyde)³⁰ or with an E-nose that can distinguish single components in gas mixtures with small prediction errors.³⁷

Gas mixtures

Human breath consists of >800 compounds,²⁵ so evaluation of the proposed filter-sensor system in gas mixtures is crucial. Figure 4a shows the Pt-doped SnO₂ response *with filter* to two consecutive 30 s exposures of simultaneous 500 ppb isoprene and acetone (grey-shaded). Most interestingly, two distinct responses are observed for each exposure. The first one increases immediately upon exposure, stays stable at ~3 and rapidly decreases after it. It is associated *solely* to isoprene, as evident from *single* isoprene exposure at the same conditions (blue line, Figure 4b) resulting in an *identical* response profile. The second response in Figure 4a is delayed, starting after ~40 s and spreading out over a couple of minutes. This

response is related to acetone. In fact, it is identical to single acetone exposure (red line, Figure 4b) and the breakthrough time, t_5 , similar to longer exposures (Figure 3c). As a result, the outstanding separation properties of the filter are preserved also in binary mixtures and isoprene is detected *selectively* during such short breath-realistic exposures. Remarkable also, the filter–sensor system recovers fully within 5 min and gives repeatable signals for continuous application. Note that these results were cross-validated by a bench-top proton-transfer-reaction time-of-flight mass spectrometer (PTR-TOF-MS) (Figure S-4).

Low-ppb isoprene detection

Breath isoprene levels can be at low ppb concentration, therefore, the Pt-doped SnO₂ sensor *with filter* was exposed to low but breath-relevant isoprene concentrations of 20, 10 and 5 ppb at 90% RH (Figure 5a). The sensor rapidly responds to these levels with high signal-to-noise ratio (>90) and can distinguish them clearly. When flushed with air, the filter–sensor system quickly regenerates (within 3 min) the original baseline and gives identical responses after repeated exposures to 20 and 10 ppb, indicating excellent reproducibility.

This filter–sensor system is applicable over the entire breath-relevant concentration range of isoprene from 5 to 500 ppb at 90% RH (blue crosses in Figure 5b). The resulting sensor responses follow a power law ($S \sim c^n$ with $n = 0.64$, $R^2 > 0.995$), in agreement with non-linear diffusion-reaction theory.⁵⁶ Remarkably as well, the presence of the filter does not compromise the sensor response to isoprene in comparison to that *without filter* (Figure 5b, red circles).

Operational stability with simulated breath pulses

To challenge the filter–sensor system further, operational stability was evaluated during continuous operation for eight days at 90% RH. To simulate daily breath isoprene measurement, three consecutive pulses of a gas mixture containing breath-median

concentrations of isoprene (106 ppb)⁴⁴, acetone (477 ppb)⁴⁵, methanol (461 ppb)⁵⁷ and ammonia (833 ppb)⁴⁵ were applied daily. Figure 6a shows the sensor responses during such a measurement cycle after six days. Isoprene is registered quickly and accurately from the first plateau during the exposure while all polar analytes are held back resulting in a delayed and accumulated spread response, similar to binary mixtures (Figure 4a). This enables precise measurement of isoprene even after several days of continuous operation despite the more concentrated interferants. Indeed, when evaluating the sensor baseline (red circles in Figure 6b) and isoprene response resistance (blue squares) during these eight days, both are quite stable (<6% change), corresponding to a change in sensor response <20% (Figure S-5). This is consistent with previous results on Pt-doped SnO₂ sensors *without filters* when operated for 20 days,⁵⁸ and could be corrected by an additional processing algorithm.⁵⁹ The filter should not contribute to this drift since it regenerates completely after each simulated breath exposure (Figure 6a), as confirmed by bench-top PTR-TOF-MS (Figure S-4). Consequently, the filter–sensor system is promising for breath isoprene measurement, but this needs to be confirmed with tests on humans as was done recently²⁴ with acetone and Si-doped WO₃ sensors to monitor body fat burn during exercise and rest.

Conclusions

A filter–sensor concept was introduced for rapid and highly selective isoprene detection in breath-relevant gas mixtures. The filter is a packed bed of activated alumina offering large surface area to retain hydrophilic compounds without affecting hydrophobic isoprene. As proof-of-concept, filters of activated alumina turned a highly sensitive, non-specific Pt-doped SnO₂ sensor *isoprene-selective* (>100) to breath-relevant acetone, ammonia, ethanol and methanol at 90% RH. That way, isoprene is detected selectively down to 5 ppb within seconds, more than sufficient for real-time breath analysis. Even when operated continuously for eight days, this filter–sensor system showed stable performance with reproducible

(regeneration within 10 min) and accurate isoprene detection in simulated breath mixtures.

Based on their small size and modular design, they can be integrated readily into inexpensive and portable breath analyzers promising for non-invasive monitoring of blood cholesterol levels and other patho/physiological conditions.

Supporting Information

The following files are available free of charge:

Supporting Information for Publication. Full sensor responses with filter for acetone, ethanol, methanol and ammonia, results at different filter loadings, sensor response with filter at different relative humidity, proton-transfer-reaction time-of-flight mass spectrometer analysis results, stability of sensor response during eight days of testing.

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Figure & Captions

Figure 1. Filter–sensor concept of selective isoprene detection in complex gas mixtures: **(a)** Breath is filtered through a packed bed filter upstream of a highly sensitive but non-specific gas sensor. **(b)** Hydrophilic analytes (e.g. acetone, ammonia, ethanol, methanol, etc.) are adsorbed and retained on the activated alumina and on the adsorbed water layer. In contrast, hydrophobic isoprene does not interact with the filter. This enables highly selective isoprene detection at low ppb concentration in real-time.

(show double column)

Figure 2. Schematic of the activated alumina filter (a) and the gas measurement setup (b).

(show single column)

Figure 3. The responses of a Pt-doped SnO₂ sensor at 90% RH to 500 ppb of isoprene (blue), acetone (red), ethanol (orange), methanol (green) and ammonia (purple) without **(a, b)** and with a 1 g activated alumina filter **(c, d)**. The single Pt-doped SnO₂ sensor without filter is rather non-specific when evaluating the responses after 30 s **(b)**. Error bars indicate the response variability of three such sensors, which is smaller than 10%. Using the filter, hydrophilic analytes are held back until their characteristic breakthrough time t_5 , while the response of isoprene is unchanged **(c)**. This results in very high isoprene-selectivity (>100) when evaluated, for instance, after 30 s **(d)**.

(show double column)

Figure 4. (a) Pt-doped SnO₂ sensor response with filter to a gas mixture of 500 ppb isoprene and acetone at 90% RH. Two consecutive pulses of 30 s (grey-shaded) were applied at 0 and 4.5 min, simulating breath pulses. (b) The single gas responses to 500 ppb of isoprene (blue) and acetone (red) at 90% RH.

(show single column)

Figure 5. (a) Pt-doped SnO₂ sensor response with filter upon exposure to 5, 10 and 20 ppb of isoprene at 90% RH. These ultra-low but breath-relevant concentrations are detectable, reproducible and clearly distinguishable (signal-to-noise ratio >90). The filter quickly and fully regenerates after each pulse. (b) Sensor response curves without (red circles) and with filter (blue crosses) over the entire breath-relevant concentration range of isoprene from 5 to 500 ppb at 90% RH.

(show single column)

Figure 6. (a) Response of Pt-doped SnO₂ with filter to three consecutive 30 s pulses of simulated breath composed of 106 ppb isoprene, 477 ppb acetone, 461 ppb methanol and 833 ppb ammonia at 90% RH on the sixth day of continuous monitoring. (b) Evolution of the sensor baseline resistance (red circles) and the isoprene response resistance (blue squares) during eight days of continuous operation and daily simulated breath analysis.

(show single column)

For TOC only