EHzürich

Research Collection



Doctoral Thesis

Selective gas sensors from flames for breath analysis

Author(s): Güntner, Andreas T.

Publication Date: 2017

Permanent Link: https://doi.org/10.3929/ethz-b-000181653 →

Rights / License: In Copyright - Non-Commercial Use Permitted →

This page was generated automatically upon download from the <u>ETH Zurich Research Collection</u>. For more information please consult the <u>Terms of use</u>.

Diss. ETH No. 23990

Selective gas sensors from flames for breath analysis

A thesis submitted to attain the degree of DOCTOR OF SCIENCES of ETH ZÜRICH

(Dr. sc. ETH Zurich)

presented by ANDREAS GÜNTNER MSc ETH Zürich born on 23.07.1987 citizen of Germany

accepted on the recommendations of Prof. Dr. Sotiris E. Pratsinis, examiner Prof. Dr. Christofer Hierold, co-examiner Dr. Agapios Agapiou, co-examiner

Zürich, 2017

Cover page with permission of The Royal Society of Chemistry

Acknowledgments

i

First and foremost, I am deeply grateful to my supervisor Prof. Dr. Sotiris E. Pratsinis for his excellent mentoring, enduring advice and stimulating ideas during this Ph.D. project. His joy and enthusiasm for research has convinced me to start this Ph.D. and was always a motivation to move on, even in tough times. I would also like to express my gratitude to Prof. Dr. Christofer Hierold and Dr. Agapiou for stimulating discussions and co-advising this thesis.

This work was performed at the Particle Technology Laboratory at ETH Zurich and I would like to thank his members for the cheerful atmosphere and the numerous fruitful discussions. I am especially thankful to Dr. Marco Righettoni who introduced me to the field of gas sensing, René Pluss who always found creative solutions and never got tired to realize new technical constructions, Dr. Frank Krumeich and Christoph Blattmann for their great help to visualize particles and films and Dr. Karsten Wegner for advice with the zeolite membranes.

Many thanks go to Prof. Dr. Malcolm Kohler, Noriane Sievi, Franziska Lettau and Anna Stöberl from the Department of Pulmonology at the University Hospital Zurich who opened the door to the clinical world with their professional help on human testing and who made ethical approvals seem suddenly very simple. I would also like to thank Sebastian Eberle and Dr. Kiran Chikkadi from the Chair in Micro- and Nanosystems at ETH Zurich for their support and advice with sensor miniaturization and inspiring discussions in all aspects of gas sensing. Many thanks go to Prof. Dr. Terence H. Risby from the Johns Hopkins University for fruitful discussions about the correct way to sample breath and Alessandro Ragnoni from the Loccioni Group for productive exchange about prototype development.

This work would not have been possible without the great commitment of bachelor and master students that did projects with me or worked as assistants and contributed to this thesis: Nicolay Pineau, Sebastian Abegg, Jonathan Theodore, Samuel Regli, Daniel Gehrig, Stéphanie Schon, Gustav Bredell, Julia Kompalla, Tobias Gulich, Vitaly Koren and Donovan Chie.

Finally, I would like to express my deepest gratitude to my family for their enduring support in every step that I make and to my beloved wife Agnes and daughter Marilena for their unconditional love and the great joy they bring into my life.

Financial support by the Swiss National Science Foundation (SNF 200021_159763/1) and the European Research Council under the European Union's Seventh Framework Program (FP7/2007-2013 247283) is gratefully acknowledged.

Contents

Ack	nowle	dgments	i		
Con	itents		iii		
Sun	nmary		ix		
Zus	amme	nfassung	xiii		
1.	Nanostructured chemoresistive gas sensors systems for breath				
	anal	ysis: potential and challenges	1		
	1.1	Breath analysis and key breath markers	1		
	1.2	Analytical methods in breath analysis	3		
	1.3	Chemoresistive metal-oxide gas sensors systems	4		
	1.4	References	6		
2.	Sele	ctive sensing of NH_3 by Si-doped α -MoO ₃ for breath	h		
	anal	ysis	13		
	2.1	Introduction	14		
	2.2	Experimental	16		
		2.2.1 Particle and sensor fabrication	16		
		2.2.2 Particle characterization	17		
		2.2.3 Sensor characterization	19		
	2.3	Results and discussion	21		
		2.3.1 Particle characterization and MoO_x phase dynamics	21		
		2.3.2 Thermal stabilization	25		
		2.3.3 Sensor performance in dry air	29		

		2.3.4 Sensor performance in humid air	32		
	2.4	Conclusions	33		
	2.5	References	34		
3.	Sele	ctive sensing of isoprene by Ti-doped ZnO for breath			
	diagnostics				
	3.1	Introduction	42		
	3.2	Experimental	43		
		3.2.1 Particle and sensing film production	43		
		3.2.2 Particle and film characterization	44		
		3.2.3 Gas sensing	46		
		3.2.4 In-situ surface characterization during sensing	47		
	3.3	Results and discussion	48		
		3.3.1 Nanostructured Ti-doped ZnO solid solutions from			
		flames	48		
		3.3.2 Crystal phase dynamics and Ti incorporation			
		mechanism	48		
		3.3.3 Ti-doping effect on particle/crystal size, morphology			
		and thermal stability	52		
		3.3.4 Selective isoprene detection by Ti-doped ZnO	56		
		3.3.5 Isoprene interaction with surface species during			
		sensing	59		
		3.3.6 Lower detection limit and sensitivity at optimal			
		sensor composition	61		
	3.4	Conclusions	63		
	3.5	References	63		

high relative humidity for breath screening of lung cancer? 71

	4.1	Introduction		
	4.2	Experimental and methods	74	
		4.2.1 Microsubstrate fabrication	74	
		4.2.2 Sensing film production	75	
		4.2.3 Sensor and E-nose evaluation	76	
		4.2.4 Data analysis	77	
	4.3	Results and discussion	79	
		4.3.1 Microsensor characterization	79	
		4.3.2 Operational temperature and single sensor stability	80	
		4.3.3 Low-ppb FA detection	82	
		4.3.4 Selectivity of single sensors	85	
		4.3.5 E-nose sensing in 2-analyte mixtures	86	
		4.3.6 3- and 4-analyte mixtures	90	
	4.4	Conclusions	92	
	4.5	References	93	
5.	Zeoli	te membranes for highly selective breath sensors	99	
	5.1	Introduction	100	
	5.2	Experimental	102	
		5.2.1 Membrane fabrication	102	
		5.2.2 Membrane characterization	103	
		5.2.3 Sensor fabrication	103	
		5.2.4 Gas detector evaluation	104	
	5.3	Results and Discussion	105	
		5.3.1 Membrane and sensor characterization	105	
		5.3.2 Zeolite membrane turn sensor formaldehyde selective	106	
		5.3.3 Separation mechanism of membrane	109	
		5.3.4 Formaldehyde monitoring and lower detection limit	110	

	5.4	Conclusions	113			
	5.5	References	114			
6.	Bod	Body fat burn monitoring from exhaled acetone with Si-				
	doped WO ₃ sensing nanoparticles					
	6.1	Introduction	120			
	6.2	Experimental	121			
		6.2.1 Acetone sensor fabrication and film characterization	121			
		6.2.2 Breath sampler design	122			
		6.2.3 Breath and blood analysis	122			
		6.2.4 Study design	123			
	6.3	Results and discussion	124			
		6.3.1 Breath acetone sensor design	124			
		6.3.2 Breath sampling and analysis strategy	126			
		6.3.3 Individual body fat burn monitoring during exercise				
		and rest	127			
	6.4	4 Conclusions				
	6.5	References				
7.	Research Recommendations					
	7.1	References	139			
A.	E-no	ose 2.0: towards orthogonal sensor arrays for improved	ł			
	analyte estimation in mixtures					
	A.1	Introduction	142			
	A.2	Experimental	144			
		A.2.1 Particle and sensor fabrication	144			
		A.2.2 Sensor evaluation	145			
		A.2.3 Data Analysis	146			

	A.3	Results and o	liscussio	n			147
		A.3.1 Sensor	· selectiv	ity and E-r	nose orthogo	onality	147
		A.3.2 E-nose	e perform	ance in ga	s mixtures		150
	A.4	Conclusions					152
	A.5	References					153
B.	Supj	olementary	Data:	E-nose	sensing	of lo	w-ppb
	forn	aldehyde in	gas mixt	tures at h	igh relative	e humidit	y for
	brea	th screening o	of lung c	ancer?			157
C.	Supplementary Data: Zeolite membranes for highly selective					ective	
	brea	th sensors					161
	C.1 \$	Sensor chambe	er design				161
	C.2 \$	Selectivity con	nparison				162
	C.3 \$	Selectivity at h	igher an	alyte conce	entrations		163
	C.4]	References					164
D.	Supplementary Data: Body fat burn monitoring from exhaled						
	acet	one with Si-do	oped WO	D ₃ sensing	nanopartic	les	165
	D.1	Physiological of	data of su	ubjects			165
	D.2]	Breath acetone	profiles	of 20 volu	inteers		166
	D.3	Breath acetone	concent	rations by	PTR-TOF-I	MS	167
	D.4]	Bland-Altman	analysis				168
Cur	riculu	m Vitae					169
Pub	licatio	ns and Preser	itations				170
Serv	vices						175

Summary

Breath analysis represents a promising method for non-invasive and rapid medical diagnostics and monitoring. Particularly interesting are handheld, simple-in-use and inexpensive breath analyzers that could enable, for instance, rapid lung cancer screening of widespread populations or daily monitoring of health parameters in real-time. Compact gas sensors could facilitate such devices, however, their application is currently limited mainly by insufficient selectivity. In this thesis, novel gas sensing materials, sensor arrays (E-noses) and filter membranes are presented that exhibit unprecedented selectivity to target breath markers.

Chapter 1 introduces the concept of breath analysis and highlights its potential and challenges, in particular for chemoresistive gas sensors. Such type of sensors are discussed in more detail by elaborating their sensing mechanism, applied materials and sensor configurations with specific focus on aspects that affect selectivity.

For some breath markers, selectivity can be found in unique material compositions of the gas sensor. Therefore, chapter 2 presents the development of *ammonia-selective Si-doped MoO*₃ gas sensors. Ammonia is an important breath marker for non-invasive detection of end-stage renal disease (ESRD) and monitoring of hemodialysis. Such sensing films are made by FSP and a tailored thermal treatment leads to highly crystalline α -MoO₃, a phase that exhibits the desired ammonia selectivity. A key novelty is the thermal stabilization of MoO₃ by Si-doping that inhibits sintering at

elevated sensing temperature for stable operation. By optimizing the dopant content and operational temperature, this sensor shows superior NH₃ selectivity towards breath-relevant acetone, NO and CO, and accurately detects breath-relevant NH₃ concentrations down to 400 ppb under breath-relevant 90% relative humidity (RH).

In chapter 3, novel *Ti-doped ZnO* gas sensors are introduced that enable *selective isoprene* detection for easy monitoring of blood cholesterol from breath. During flame synthesis, Ti is either incorporated into the ZnO wurtzite lattice or dispersed on the particle surface as revealed by crystallographic analysis and electron microscopic characterization. These point defects enhance the isoprene response and turn ZnO isoprene-selective as supported by in-situ infrared spectroscopy. An optimal Ti content is identified and this sensor shows superior isoprene responses compared to acetone, NH₃ 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 (SNR).

Formaldehyde (FA) is a promising lung cancer breath marker, and no sensing material with sufficient FA selectivity had been found yet. To overcome this, a highly sensitive, selective and compact *electronic nose* (Enose) is presented in chapter 4. This E-nose comprises four flame-made and differently doped (Pt, Si, Pd and Ti) SnO₂ sensing films directly deposited onto silicon wafer-based microsubstrates. Each dopant induces different analyte selectivity and together with statistical response analysis by multivariate linear regression, combinatorial FA selectivity is obtained. In fact, this E-nose can estimate FA with an average error \leq 9 ppb in simulated breath (FA with higher acetone, NH₃ and ethanol concentrations) at 90% RH overcoming selectivity issues of single sensors.

Also filters can enhance the selectivity of gas sensors. In chapter 5, a novel concept for highly selective breath sensors is proposed that combines *membranes* to pre-separate the microporous gas mixture with а chemoresistive gas sensor to detect the target analyte. As proof-of-concept, a compact zeolite Mobil-Five (MFI)/Al₂O₃ membrane is placed upstream of a highly sensitive but weakly selective, nanostructured Pd-doped SnO₂ sensor. In fact, this system exhibits excellent selectivity (> 100) to FA over ethanol, ammonia, acetone and isoprene even in gas mixtures at 50% RH, superior to existing sensors. Moreover, FA concentrations down to 30 ppb are detected, sufficiently low for breath analysis. This novel concept can be extended to other tracers and it could facilitate a new class of selective and portable gas detectors.

Finally in chapter 6, flame-made breath sensors are *applied on humans*. Monitoring acetone from breath can assist to lose body fat more effectively by guiding exercise and dieting to optimal conditions. Therefore, a portable, simple-in-use and inexpensive breath acetone detector is presented and applied to 20 volunteers during exercise and rest to monitor their fat burn intensity. The detector combines a highly sensitive acetone sensor consisting of Si-doped WO₃ nanoparticles with a breath sampler for monitored and reproducible breath sampling. During the testing course, this detector indicates clearly the onset and progression of acetone increase during and after exercise, in good agreement (Pearson's 0.97) to simultaneously PTR-TOF-MS measurements. In parallel sampled blood BOHB correlates well (Pearson's 0.831) to sensor-detected breath acetone supporting the sensor's suitability as non-invasive fat burn detector. As a result, this simple breath analyzer can facilitate easily applicable and hand-held fat burn monitors for gyms to provide immediate feedback on workout effectiveness or to guide dieting.

In breath analysis, the application of gas sensors was mainly limited by their lack of selectivity. In this thesis, it is shown how sensing films, their combination in E-noses and additional microporous membranes can be systematically developed and combined for the selective detection of important breath markers. With an appropriate sampler design, such breath sensor can be readily applied for breath analysis exhibiting promising results.

Zusammenfassung

Die Atemgasanalyse ist eine vielversprechende Methode für nichtinvasive und rasche Medizinaldiagnostik und Überwachung. Besonders leicht interessant sind tragbare, verwendbare und preiswerte Atemgasdetektoren. Diese könnten beispielweise ein rasches Lungenkrebsscreening grosser Population ermöglichen oder die tägliche Überwachung wichtiger Körperparameter vereinfachen. Kompakte Gassensoren könnten solche Geräte ermöglichen, deren Verwendung ist derzeit jedoch noch durch unzureichende Selektivität limitiert. In dieser Arbeit werden neuartige Materialien für Gassensoren, "Arrays" und Filter vorgestellt, welche bisher unerreichte Selektivität wichtigen zu Atemmarkern aufweisen.

In Kapitel 1 wird das Konzept der Atemgasanalyse vorgestellt, wobei Chancen und Herausforderungen, im Speziellen für chemoresistive Gassensoren, hervorgehoben werden. Dieser Sensortyp wird detailliert mit Erläuterungen zum Sensormechanismus, verwendete Materialien und deren Konfiguration beschrieben. Spezielles Augenmerk wird dabei auf Aspekte gelegt, welche die Selektivität beeinflussen.

Für einige Atemmarker kann Sensorselektivität durch gezielte Wahl der Materialzusammensetzung erreicht werden. Kapitel 2 stellt die Entwicklung *ammoniakselektiver Si-dotierten MoO₃-Sensoren* vor. Ammoniak ist ein wichtiger Atemmarker für die nicht-invasive Erkennung chronischen Nierenversagens und kann auch zur Überwachung bei der Blutdialyse verwendet werden. Diese ammoniakselektiven Sensorfilme werden mit FSP hergestellt. Eine mass-geschneiderte, thermische Nachbehandlung führt zu hochkristallinem a-MoO₃, einer Kristallphase welche die gewünschte Ammoniakselektivität aufweist. Eine wichtige Neuheit ist dabei die thermische Stabilisierung von MoO₃ durch Si-Dotierung, die das Sintern der Nanopartikel bei hohen Sensorbetriebstemperaturen verhindert und somit stabilen Betrieb gewährleistet. Durch die Optimierung des Si-Gehalts und erreicht der Sensor der Sensorbetriebstemperatur überragende Ammoniakselektivität gegenüber anderen Atemkomponenten wie Azeton, NO und CO. Gleichzeitig kann diese Sensor atemrelevante 90% Ammoniakkonzentrationen bis auf 400 bei relativer ppb Luftfeuchtigkeit (RH) exakt detektieren.

Kapitel 3 behandelt neuentwickelte Ti-dotierte ZnO-Gassensoren, welche Isopren selektiv detektieren können. Isopren kann zur nicht-Überwachung von Blutcholesterin durch invasiven Atemgasanalyse verwendet werden. Während der Flammensynthese wird das Ti entweder in das Zn-Wurzitkristallgitter eingelagert oder an der Oberfläche der ZnO-Nanopartikel dispergiert, wie mit Hilfe kristallografischer Analyse und elektronischenmikroskopischer Charakterisierung nachgewiesen wird. Diese Punktdefekte verstärken das Signal des Ti-dotierten ZnO Gassensors auf Isopren was zu verbesserter Selektivität führt, wie durch in-situ Infrarotspektroskopie nachgewiesen wird. Ein optimaler Ti-Gehalt wird identifiziert welcher dem Sensor überragende Signalstärke für Isopren mit hoher Selektivität gegenüber Azeton, Ethanol und Ammoniak bei 90% RH verleiht Bemerkenswert dabei ist. dieser dass Sensor Isoprenkonzentrationen bis auf 5 ppb exakt und mit grossem (< 10) Signal-Rausch-Verhältnis detektieren kann.

Formaldehvd ist ein vielversprechender Atemmarker für Lungenkrebs, allerdings gibt es derzeit kein bekanntes Sensormaterial das genügend Formaldehydselektivität aufweist. Für die Messung von Formaldehyd wird daher in Kapitel 4 eine hochsensitive, selektive und kompakte elektronische Nase ("*E-nose*") vorgestellt. Diese E-nose besteht aus vier SnO₂-Sensoren mit jeweils unterschiedlicher Dotierung (Pt, Si, Pd und Ti) welche durch Flammensynthese direkt auf Silikonwafer-basierte Mikrosubstrate abgelagert werden. Jedes Dotierungselement induziert verschiedene Selektivitätsänderungen, welche dann mittels statistischer Signalanalyse multivariate durch lineare Regression zu kombinatorischer Formaldehydselektivität führt. Diese E-nose kann Formaldehyd mit einem gemittelten Fehler \leq 9 ppb in simulierter Atemluft (Formaldehyd in einem Gasgemisch mit höher konzentriertem Azeton, Ammoniak und Ethanol in 90% RH) selektiv detektieren und dadurch die Selektivitätsprobleme alleinstehender Gassensors überwinden.

Auch Filter können die Selektivität von Gassensoren verbessern. In Kapitel 5 wird daher ein neues Konzept vorgeschlagen, welches hochselektive Gassensoren für die Atemgasanalyse ermöglichen soll. Dabei werden mikroporöse Membrane zur Separation eines komplexen Gasgemisches mit chemoresistiven Gassensoren kombiniert. In einer Machbarkeitsstudie wird daraufhin eine kompakte Membran, bestehend aus dem Zeolithe "Mobile-Five (MFI)" und Al₂O₃, vor einem hochsensitiven, aber nur schwach selektiven Pd-dotierten SnO₂ Sensor eingebaut. Dies resultiert in exzellenter (> 100) Formaldehydselektivität in Gasgemischen mit Ethanol, Ammoniak, Azeton und Isopren bei 50% RH, was allen existierenden Formaldehydsensoren überlegen ist. Mit diesem System können Formaldehydkonzentrationen bis auf 30 ppb detektiert werden, genügend tief für die Atemgasanalyse. Dieses neuartige Konzept kann auch

auf andere Gase angewendet werden und dies könnte eine neue Generation selektiver und tragbarer Gasdetektoren ermöglichen.

In Kapitel 6 werden dann flammenhergestellte Gassensoren an Menschen getestet. Atemazeton kann dabei helfen Sport und Diät unter optimalen Bedingungen zu betreiben, um Körperfett effizienter abzubauen. Hierfür wird ein tragbarer, einfach anwendbarer und kostengünstiger Atemazetondetektor entwickelt und während physischer Belastung sowie im Ruhezustand an 20 Probanden getestet um deren Fettverbrennung zu überwachen. Der Detektor besteht einerseits aus einem hochsensitiven Azetonsensor aus Si-dotierten WO₃-Nanopartikeln und andererseits aus einem speziell angefertigten Atementnahmegerät welches überwachte (Atemluftdruck, Ausatmungsstrom und CO₂-Gehalt) und reproduzierbare Atemproben ermöglicht. Dieser Detektor ist in der Lage, den Beginn sowie den Verlauf ansteigender Azeton-konzentrationen während und nach physischer Belastung zu messen. Die gemessenen Werte korrelieren gut (Pearson-Korrelationkoeffizient 0.97) mit zeitgleichen Messungen mittels Proton-Transfer-Reaction Time-of-Flight Massenspektrometer. Parallel dazu wurde der Blutgehalt von β -hydroxybutyrate (BOHB) gemessen und dieser korreliert gut zu den vom Sensor gemessenen Atemazetonkonzentrationen. Der hier präsentierte Atemdetektor hat grosses Potential für die Verwendung als kostengünstiger, einfach anwendbarer und tragbarer Fettverbrennungsdetektor in Sportstudios während des Trainings oder um Diät zu unterstützen.

Bisher war der Einsatz von Gassensoren in der Atemgasanalyse durch deren schwache Selektivität begrenzt. In dieser Arbeit wird gezeigt, wie Sensormaterialien optimiert, sowie Sensoren zu E-noses und mit mikroporösen Membranen systematisch kombiniert werden können um selektive Detektion von Atemmarkern zu ermöglichen. Mit einem zweckmässigen Atementnahmegerät sind solche Sensorsysteme dann direkt für die Atemanalyse verwendbar, was unmittelbar zu vielversprechenden Ergebnissen führt.

Nanostructured chemoresistive gas sensors systems for breath analysis: potential and challenges

1.1 Breath analysis and key breath markers

Rapidly increasing health care expenses stimulate innovation for nextgeneration techniques that enable cost-effective medical diagnostics and monitoring.¹ Breath analysis is a promising candidate since it is noninvasive (thus inherently safe), rapid and easily applicable.² In principle, breath analysis relies on the concept that physiological and pathological information is contained in the composition of breath³ reflecting the blood chemistry via exchange in the lung and airways.⁴ So far, several hundreds of volatile organic compounds and other gases have been identified in breath⁵ with some being correlated to metabolic processes and diseased states, socalled breath markers.²

Particular promising is breath ammonia (NH₃), that is present at typical mouth-exhaled concentrations of 400 - 1800 parts-per-billion (ppb) and a product of the protein metabolism⁶. Abnormal levels are symptomatic for end-stage renal disease (ESRD) where breath levels may even exceed 10'000 ppb.⁶ Since breath ammonia correlates well with blood urea nitrogen (BUN), it has been proposed as tracer to monitor hemodialysis non-invasively and in real-time.⁶⁻⁹ Altered NH₃ concentrations were identified as well in patients suffering from hepatic dysfunction (e.g. hepatic injury,¹⁰ cirrhosis¹¹ and hepatic encephalopathy¹¹), bacterial infection by *Helicobacter Pylori¹²* and halitosis.¹³

Endogenous isoprene is a potential marker to monitor high blood cholesterol levels and their therapy.¹⁴ Being a by-product of the cholesterol synthesis,¹⁴ breath isoprene follows the dynamic of blood cholesterol when treating patients with cholesterol-lowering lova-¹⁵ and atorastatins.¹⁶ Typical isoprene breath concentrations are in the range of 22 to 234 ppb¹⁷ while changes were recognized also during physical activity,¹⁸ ESRD,¹⁹ advanced fibrosis in liver disease patients²⁰ and lung cancer.²¹

Breath acetone in mammals is produced during lipolysis²² and is therefore an indicator for fat burn.²³ While its typical concentration in exhaled breath varies in the range of 150 and 2750 ppb,²⁴ it increases significantly during exercise (cycling²⁵ and walking²⁶) and ketogenic diet²⁷ reflecting the enhanced fat break-down. Elevated acetone levels were observed also in type-1 diabetics²⁸ as a result of the disordered metabolism.

Studies on lung cancer patients suggest that there is no single breath marker but rather a pattern of compounds.^{21, 29, 30} These can be categorized into seven chemical families (hydrocarbons, alcohols, aldehydes, ketones, esters, nitriles and aromatic compounds) that are related to specific pathological processes.²⁹ For instance aldehydes show distinct changes and can be used to distinguish lung cancer patients from healthy individuals.³¹

So far, only few breath tests are actively applied in clinical practice, including the breath ethanol tests,² CO₂ monitoring in intensive care and anesthesia³², ^{13/14}C urea test for the diagnosis of *Helicobacter Pylori*³³ and FeNO to detect inflammatory conditions of the airways (e.g. asthma).³⁴ For most diagnostic decisions, however, invasive methods (e.g. blood assay) remain the "golden standard" despite the evident potential of breath analysis.² This stimulates research to develop suitable breath analyzers that can accurately detect and monitor target breath markers.

1.2 Analytical methods in breath analysis

Breath analysis is a challenging task for analytical devices. In fact, single breath markers need to be detected at trace levels with high selectivity to other breath compounds and in the presence of high relative humidity (typically 89 - 97%³⁵).³⁶ Currently applied technologies can be divided primarily into three categories:³⁷ mass spectrometry- (MS) or gas chromatography-based (GC) techniques, laser-adsorption spectroscopic methods and chemical sensors. Most common is GC³⁸ that can be coupled with various detection methods, including MS³⁹, flame ionization detection⁴⁰ or ion mobility spectrometry⁴¹. However, a major drawback of GC-based methods represents their incapability to analyze breath in real-time.

Therefore, more sophisticated techniques had been developed that can detect a large number of breath compounds in real-time with high selectivity and sufficient low detection limit. These include proton transfer reaction mass spectrometry (PTR-MS),^{42, 43} proton transfer reaction time-of-flight mass spectrometry (PTR-TOF-MS)^{44, 45} and selective ion flow tube mass spectrometry (SIFT-MS)⁴⁶. However, all these devices are limited in portability, complex in application and expensive, thus hardly suitable for portable breath analyzers for daily monitoring of body health parameters (e.g. BUN or cholesterol) or to guide exercise in gyms for effective fat loss.

For this purpose, chemoresistive gas sensors based on metal-oxides (MOx) are especially attractive since they feature low fabrication costs,⁴⁷ simple applicability³⁷ and can be miniaturized extremely⁴⁸ to fit into portable breath analyzers.⁴⁹ However to apply such sensors to human breath, some characteristics need to be developed, i.e. high sensitivity, sufficiently low detection limit and, most difficult to achieve, selectivity to the target marker in the complex mixture of breath at high relative humidity.

1.3 Chemoresistive metal-oxide gas sensors systems

The sensing mechanism of chemoresistive MOx gas sensors is based on resistance changes when exposed to an analyte. In specific, reducing or oxidizing gases interact with chemisorbed oxygen species on the MOx surface and change their surface concentration.⁵⁰ This results in charge carrier injection or removal modulating the resistance of the semiconductive MOx film that is detected as signal.⁵¹ Typically, the MOx sensing layers are highly porous films to facilitate rapid analyte diffusion into the sensing structure for fast response and recovery times.⁵¹

High sensitivity and sufficiently low detection limit for breath analysis can be achieved by refining the sensing structure to the nanoscale.⁵² That way, large specific surface area is provided to interact with analyte molecules.⁵³ Furthermore, narrowing the sensing structures to dimensions approaching twice the MOx's Debye length leads to exceptionally high sensitivity.⁵⁴ That way, breath markers can be detected at trace-level concentrations, as shown for acetone down to 20 ppb at 90% RH with Sidoped WO₃.⁵⁵

Selectivity is strongly influenced by the choice of material. While wellknown MOx materials (e.g. SnO_2)⁵⁶ lack selectivity, it can be found in unprecedented material compositions resulting in metastable phases (e.g. ϵ -WO₃⁵⁷), unique morphologies, solid solutions or mixed oxides. Optimizing the operational temperature can improve selectivity even further. In fact, MOx gas sensors go through response maxima when increasing the temperature,⁵⁸ and optimal conditions are found for each material-analyte combination individually.

Selectivity issues of sensing materials can be tackled also by introducing supporting components, as shown Figure 1.1. A viable option is to combine several sensors that may feature weak but should possess different selectivity to sensor arrays, so-called electronic noses (E-nose).⁵⁹ Combinatorial selectivity is obtained by statistical response analysis for patterns recognition^{30, 60} or to quantify single analytes.⁶¹



Figure 1.1: Components of a chemoresistive metal-oxide gas sensor system affecting selectivity.

Promising to remove undesirable confounders are additional filters (Figure 1.1) to pre-separate the gas mixture.⁶² These can be realized as membranes, packed bed⁶³ or even applied as coating directly on the sensing material.⁶⁴ Applied filter materials include active carbon⁶³ and polymers (e.g. Nafion⁶⁵) while microporous materials (e.g. zeolite and metal-organic frameworks⁶⁴) are promising alternatives featuring widely tunable⁶⁶ separation properties.

In this thesis, novel gas sensing materials, sensor arrays (E-noses) and filter membranes are explored and systematically developed to meet the selectivity and sensitivity requirements for key breath markers in breath analysis and finally tested on humans.

1.4 References

- [1] W. Miekisch, J. K. Schubert and G. F. E. Noeldge-Schomburg, Diagnostic potential of breath analysis—focus on volatile organic compounds, *Clin. Chim. Acta*, **2004**, 347, 25-39.
- [2] T. H. Risby and S. F. Solga, Current status of clinical breath analysis, *Appl. Phys. B*, **2006**, 85, 421-426.
- [3] A. Amann, P. Spanel and D. Smith, Breath analysis: the approach towards clinical applications, *Mini reviews in Medicinal Chemistry*, **2007**, 7.
- [4] A. Manolis, The diagnostic potential of breath analysis, *Clin. Chem.*, **1983**, 29.
- [5] B. De Lacy Costello, A. Amann, H. Al-Kateb, C. Flynn, W. Filipiak, T. Khalid, D. Osborne and N. M. Ratcliffe, A review of the volatiles from the healthy human body, *J. Breath Res.*, 2014, 8, 014001.
- [6] S. Davies, P. Spanel and D. Smith, Quantitative analysis of ammonia on the breath of patients in end-stage renal failure, *Kidney Int.*, **1997**, 52, 223-228.
- [7] L. R. Narasimhan, W. Goodman and C. K. N. Patel, Correlation of breath ammonia with blood urea nitrogen and creatinine during hemodialysis, *Proc. Natl. Acad. Sci. U. S. A.*, **2001**, 98, 4617-4621.
- [8] T. Hibbard, K. Crowley, F. Kelly, F. Ward, J. Holian, A. Watson and A. J. Killard, Point of Care Monitoring of Hemodialysis Patients with a Breath Ammonia Measurement Device Based on Printed Polyaniline Nanoparticle Sensors, *Anal. Chem.*, 2013, 85, 12158-12165.
- [9] Z. H. Endre, J. W. Pickering, M. K. Storer, W. P. Hu, K. T. Moorhead, R. Allardyce, D. O. McGregor and J. M. Scotter, Breath ammonia and trimethylamine allow real-time monitoring of haemodialysis efficacy, *Physiol. Meas.*, **2011**, 32, 115-130.
- [10] M. Z. Dai, Y. L. Lin, H. C. Lin, H. W. Zan, K. T. Chang, H. F. Meng, J. W. Liao, M. J. Tsai and H. Cheng, Highly Sensitive Ammonia Sensor with Organic Vertical Nanojunctions for Noninvasive Detection of Hepatic Injury, *Anal. Chem.*, **2013**, 85, 3110-3117.

- [11] R. Adrover, D. Cocozzella, E. Ridruejo, A. Garcia, J. Rome and J. J. Podesta, Breath-Ammonia Testing of Healthy Subjects and Patients with Cirrhosis, *Dig. Dis. Sci.*, **2012**, 57, 189-195.
- [12] D. Kearney, T. Hubbard and D. Putnam, Breath Ammonia Measurement in Helicobacter pylori Infection, *Dig. Dis. Sci.*, **2002**, 47, 2523-2530.
- [13] A. Amano, Y. Yoshida, T. Oho and T. Koga, Monitoring ammonia to assess halitosis, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 2002, 94, 692-696.
- [14] R. Salerno-Kennedy and K. Cashman, Potential applications of breath isoprene as a biomarker in modern medicine: a concise overview, *Wien*. *Klin. Wochenschr.*, 2005, 117, 180-186.
- [15] B. G. Stone, T. J. Besse, W. C. Duane, C. Dean Evans and E. G. DeMaster, Effect of regulating cholesterol biosynthesis on breath isoprene excretion in men, *Lipids*, **1993**, 28, 705-708.
- [16] T. Karl, P. Prazeller, D. Mayr, A. Jordan, J. Rieder, R. Fall and W. Lindinger, Human breath isoprene and its relation to blood cholesterol levels: new measurements and modeling, *J. Appl. Physiol.*, 2001, 91, 762-770.
- [17] P. Španěl, S. Davies and D. Smith, Quantification of breath isoprene using the selected ion flow tube mass spectrometric analytical method, *Rapid Commun. Mass Spectrom.*, **1999**, 13, 1733-1738.
- [18] J. King, A. Kupferthaler, K. Unterkofler, H. Koc, S. Teschl, W. Miekisch, J. Schubert, H. Hitnerhuber and A. Amann, Isoprene and acetone concentration profiles during exercise at an ergometer, *J Breath Res*, 2009, s3.
- [19] S. Davies, P. Španel and D. Smith, A new 'online' method to measure increased exhaled isoprene in end-stage renal failure, *Nephrol. Dial. Transpl.*, 2001, 16, 836-839.
- [20] N. Alkhouri, T. Singh, E. Alsabbagh, J. Guirguis, T. Chami, I. Hanouneh, D. Grove, R. Lopez and R. Dweik, Isoprene in the Exhaled Breath is a Novel Biomarker for Advanced Fibrosis in Patients with Chronic Liver Disease: A Pilot Study, *Clin. Trans. Gastroenterol.*, 2015, 6, e112.
- [21] A. Bajtarevic, C. Ager, M. Pienz, M. Klieber, K. Schwarz, M. Ligor, T. Ligor, W. Filipiak, H. Denz, M. Fiegl, et al., Noninvasive detection of lung cancer by analysis of exhaled breath, *BMC Cancer*, 2009, 9, 1-16.

- [22] M. P. Kalapos, On the mammalian acetone metabolism: from chemistry to clinical implications, *BBA-Gen Subjects*, **2003**, 1621, 122-139.
- [23] J. C. Anderson, Measuring breath acetone for monitoring fat loss: Review, *Obesity*, **2015**, 23, 2327-2334.
- [24] C. Turner, P. Španěl and D. Smith, A longitudinal study of ammonia, acetone and propanol in the exhaled breath of 30 subjects using selected ion flow tube mass spectrometry, SIFT-MS, *Physiol. Meas.*, **2006**, 27, 321.
- [25] K. Yamai, T. Ohkuwa, H. Itoh, Y. Yamazaki and T. Tsuda, Influence of cycle exercise on acetone in expired air and skin gas, *Redox Report*, **2013**.
- [26] D. Samudrala, G. Lammers, J. Mandon, L. Blanchet, T. H. Schreuder, M. T. Hopman, F. J. Harren, L. Tappy and S. M. Cristescu, Breath acetone to monitor life style interventions in field conditions: An exploratory study, *Obesity*, 2014, 22, 980-983.
- [27] P. Spanel, K. Dryahina, A. Rejskova, T. W. E. Chippendale and D. Smith, Breath acetone concentration; biological variability and the influence of diet, *Physiol. Meas.*, 2011, 32, N23-N31.
- [28] Z. Wang and C. Wang, Is breath acetone a biomarker of diabetes? A historical review on breath acetone measurements, *J. Breath Res.*, **2013**, 7, 037109.
- [29] M. Hakim, Y. Y. Broza, O. Barash, N. Peled, M. Phillips, A. Amann and H. Haick, Volatile organic compounds of lung cancer and possible biochemical pathways, *Chem. Rev.*, 2012, 112, 5949-5966.
- [30] G. Peng, U. Tisch, O. Adams, M. Hakim, N. Shehada, Y. Y. Broza, S. Billan, R. Abdah-Bortnyak, A. Kuten and H. Haick, Diagnosing lung cancer in exhaled breath using gold nanoparticles, *Nat. Nanotech.*, 2009, 4, 669-673.
- [31] P. Fuchs, C. Loeseken, J. K. Schubert and W. Miekisch, Breath gas aldehydes as biomarkers of lung cancer, *Int. J. Cancer*, 2010, 126, 2663-2670.
- [32] S. Y. Liu, T. S. Lee and F. Bongard, Accuracy of capnography in nonintubated surgical patients, *Chest*, **1992**, 102, 1512-1515.

- [33] J. P. Gisbert and J. M. Pajares, Review article: 13C-urea breath test in the diagnosis of Helicobacter pylori infection – a critical review, *Aliment. Pharmacol. Ther.*, 2004, 20, 1001-1017.
- [34] R. A. Dweik, P. B. Boggs, S. C. Erzurum, C. G. Irvin, M. W. Leigh, J. O. Lundberg, A.-C. Olin, A. L. Plummer and D. R. Taylor, An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications, *Am. J. Respir. Crit. Care Med.*, 2011, 184, 602-615.
- [35] L. Ferrus, H. Guenard, G. Vardon and P. Varene, Respiratory water loss, *Respir. Physiol.*, **1980**, 39, 367-381.
- [36] W. Cao and Y. Duan, Current status of methods and techniques for breath analysis, *Crit. Rev. Anal. Chem.*, **2007**, 37, 3-13.
- [37] M. Righettoni, A. Amann and S. E. Pratsinis, Breath analysis by nanostructured metal oxides as chemo-resistive gas sensors, *Mater*. *Today*, **2015**, 18, 163-171.
- [38] R. Teranishi, T. R. Mon, A. B. Robinson, P. Cary and L. Pauling, Gas chromatography of volatiles from breath and urine, *Anal. Chem.*, 1972, 44, 18-20.
- [39] M. Phillips, J. Herrera, S. Krishnan, M. Zain, J. Greenberg and R. N. Cataneo, Variation in volatile organic compounds in the breath of normal humans, *J. Chromatogr. B. Biomed. Appl.*, **1999**, 729, 75-88.
- [40] T. H. Risby, L. Jiang, S. Stoll, D. Ingram, E. Spangler, J. Heim, R. Cutler, G. S. Roth and J. M. Rifkind, Breath ethane as a marker of reactive oxygen species during manipulation of diet and oxygen tension in rats, *J. Appl. Physiol.*, **1999**, 86, 617-622.
- [41] H. Lord, Y. Yu, A. Segal and J. Pawliszyn, Breath Analysis and Monitoring by Membrane Extraction with Sorbent Interface, *Anal. Chem.*, 2002, 74, 5650-5657.
- [42] A. Hansel, A. Jordan, R. Holzinger, P. Prazeller, W. Vogel and W. Lindinger, Proton transfer reaction mass spectrometry: on-line trace gas analysis at the ppb level, *Int. J. Mass Spectrom. Ion Processes*, 1995, 149–150, 609-619.
- [43] W. Lindinger, A. Hansel and A. Jordan, On-line monitoring of volatile organic compounds at pptv levels by means of proton-transfer-reaction

mass spectrometry (PTR-MS) medical applications, food control and environmental research, *Int J Mass Spectrom Ion Processes*, **1998**, 173.

- [44] A. Jordan, S. Haidacher, G. Hanel, E. Hartungen, L. Märk, H. Seehauser, R. Schottkowsky, P. Sulzer and T. Märk, A high resolution and high sensitivity proton-transfer-reaction time-of-flight mass spectrometer (PTR-TOF-MS), *Int. J. Mass spectrom.*, 2009, 286, 122-128.
- [45] J. Herbig, M. Mueller, S. Schallhart, T. Titzmann, M. Graus and A. Hansel, On-line breath analysis with PTR-TOF, *J. Breath Res.*, **2009**, 3.
- [46] D. Smith and P. Spanel, The Novel Selected-ion Flow Tube Approach to Trace Gas Analysis of Air and Breath, *Rapid Commun. Mass Spectrom.*, 1996, 10, 1183-1198.
- [47] S. Kühne, M. Graf, A. Tricoli, F. Mayer, S. E. Pratsinis and A. Hierlemann, Wafer-level flame-spray-pyrolysis deposition of gassensitive layers on microsensors, *J. Micromech. Microeng.*, 2008, 18, 035040.
- [48] C. Hagleitner, A. Hierlemann, D. Lange, A. Kummer, N. Kerness, O. Brand and H. Baltes, Smart single-chip gas sensor microsystem, *Nature*, 2001, 414, 293-296.
- [49] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, *J. Breath Res.*, 2015, 9, 047101.
- [50] N. Yamazoe, G. Sakai and K. Shimanoe, Oxide Semiconductor Gas Sensors, *Catalysis Surveys from Asia*, **2003**, 7, 63-75.
- [51] N. Barsan and U. Weimar, Conduction Model of Metal Oxide Gas Sensors, *J. Electroceram.*, **2001**, 7, 143-167.
- [52] C. Xu, J. Tamaki, N. Miura and N. Yamazoe, Grain size effects on gas sensitivity of porous SnO₂-based elements, *Sens. Actuators B*, **1991**, 3, 147-155.
- [53] N. Yamazoe, New approaches for improving semiconductor gas sensors, *Sens. Actuators B*, **1991**, 5, 7-19.
- [54] H. Ogawa, M. Nishikawa and A. Abe, Hall measurement studies and an electrical conduction model of tin oxide ultrafine particle films, *J. Appl. Phys.*, **1982**, 53, 4448-4455.

- [55] M. Righettoni, A. Tricoli and S. E. Pratsinis, Si:WO₃ Sensors for Highly Selective Detection of Acetone for Easy Diagnosis of Diabetes by Breath Analysis, *Anal. Chem.*, **2010**, 82, 3581-3587.
- [56] J. F. McAleer, P. T. Moseley, J. O. W. Norris, D. E. Williams, P. Taylor and B. C. Tofield, Tin oxide based gas sensors, *Mater. Chem. Phys.*, 1987, 17, 577-583.
- [57] L. Wang, A. Teleki, S. E. Pratsinis and P. I. Gouma, Ferroelectric WO₃ Nanoparticles for Acetone Selective Detection, *Chem. Mater.*, 2008, 20, 4794-4796.
- [58] N. Yamazoe, Y. Kurokawa and T. Seiyama, Effects of additives on semiconductor gas sensors, *Sensors and Actuators*, **1983**, 4, 283-289.
- [59] K. Persaud and G. Dodd, Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose, *Nature*, **1982**, 299, 352-355.
- [60] C. Di Natale, A. Macagnano, E. Martinelli, R. Paolesse, G. D'Arcangelo, C. Roscioni, A. Finazzi-Agrò and A. D'Amico, Lung cancer identification by the analysis of breath by means of an array of non-selective gas sensors, *Biosens. Bioelectron.*, 2003, 18, 1209-1218.
- [61] W. P. Carey and S. S. Yee, Calibration of nonlinear solid-state sensor arrays using multivariate regression techniques, *Sens. Actuators B*, 1992, 9, 113-122.
- [62] G. Korotcenkov, *Handbook of gas sensor materials*, Springer, 2013.
- [63] M. Schweizer-Berberich, S. Strathmann, W. Göpel, R. Sharma and A. Peyre-Lavigne, Filters for tin dioxide CO gas sensors to pass the UL2034 standard, *Sens. Actuators B*, 2000, 66, 34-36.
- [64] H. Tian, H. Fan, M. Li and L. Ma, Zeolitic imidazolate framework coated ZnO nanorods as molecular sieving to improve selectivity of formaldehyde gas sensor, ACS Sens., 2016, 1, 243-250.
- [65] S. Kitsukawa, H. Nakagawa, K. Fukuda, S. Asakura, S. Takahashi and T. Shigemori, The interference elimination for gas sensor by catalyst filters, *Sens. Actuators B*, 2000, 65, 120-121.
- [66] B. Smit and T. L. Maesen, Towards a molecular understanding of shape selectivity, *Nature*, **2008**, 451, 671-678.

Selective sensing of NH_3 by Si-doped α -MoO₃ for breath analysis

Abstract Ammonia (NH₃) is an important breath marker for non-invasive detection and monitoring of end-stage renal disease (ESRD). Here, a chemoresistive gas sensor has been developed consisting of flame-made nanostructured α -MoO₃, a promising phase for selective detection of breath NH₃. A key novelty is the thermal stabilization of α -MoO₃ 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 flame spray pyrolysis (FSP) and directly deposited onto sensor substrates forming highly porous films with ribbon-like and nanoparticle/needle-like morphologies, respectively.

In-situ XRD analysis of the MoO_x phase dynamics revealed a thermally-induced recrystallization of β -MoO₃ at 300 - 350 °C and optimal annealing at 450 °C for synthesis of highly nanocrystalline α -MoO₃. For selective NH₃ sensing, however, the optimum SiO₂ content was 3 wt% and the operational temperature 400 °C. This sensor showed superior NH₃ selectivity towards acetone, NO and CO, and accurately detected breath-relevant NH₃ concentrations down to 400 ppb under 90% relative humidity (RH). As a result, a stable and inexpensive sensor for NH₃ is presented which has the potential for further development towards a handheld device for the early-stage diagnosis and monitoring of ESRD.

2.1 Introduction

Around 3 million patients worldwide suffer from end-stage renal disease (ESRD), a number that increases at ~7% annually (2012).¹ The ESRD negatively affects the patient's life expectancy with considerable impact on quality of life. The commonly applied dialysis treatment¹ only partially compensates the symptoms and forces a change in patient's lifestyle.² In addition, the treatment of ESRD is disproportionally expensive compared to other chronic diseases. For haemodialysis (HD), costs per patient in the US were estimated to be ~88'000 \$/y in 2011.³ Early detection of ESRD and real-time monitoring of its progression and therapy may improve medical treatment to a tailored point-of-care therapy⁴ with higher chance for patient recovery, better quality of life and drastic reduction of disease-related expenses.

Breath analysis represents a promising non-invasive, fast and costeffective alternative to well-established diagnostic and monitoring techniques such as blood analysis, endoscopy, ultrasonic and tomographic monitoring. NH₃ is a promising breath marker for the detection of kidney⁵ and liver diseases.⁶ More specifically, mouth-exhaled breath NH₃ levels were identified to be around 400 - 1800 ppb (mean 960) for healthy people and elevated to 820 - 14700 ppb (mean 4880) for ESRD patients,⁵ a trend consistent with other studies.^{4,7,8} Furthermore, breath NH₃ has been proposed as indicator to removal of blood urea nitrogen (BUN) since its concentration follows the BUN kinetics during dialysis treatment.^{4,5,7,8} This could enable real-time monitoring and thus on-demand tailoring of ESRD therapy. Note that the origin of mouth-exhaled breath NH₃ is still under investigation but there is evidence that it is partially generated in the oral cavity.^{9,10} Metal-oxide (chemoresistive) gas sensors are especially attractive for NH₃ detection since they offer simple operation, low power consumption and can be readily used in a portable device¹¹ compared to more sophisticated methods such as selected ion flow tube mass spectrometry (SIFT-MS)⁵ or laser photoacoustic spectroscopy (PALS).¹² However to apply such sensors to human breath, some characteristics need to be developed, i.e. high sensitivity to low NH₃ concentrations, selective detection in a complex gas mixture¹³ and low cross-sensitivity to high relative humidity (89 - 97%).¹⁴ Tailoring the material (morphology, size, phase composition) during preparation and processing, and optimizing the operational conditions are needed to meet the above requirements for sensor performance.¹⁵ Such a development has been demonstrated recently with a portable ε -WO₃ sensor as breath acetone detector¹⁶ that correlates well to blood glucose early morning before breakfast.¹⁷

The orthorhombic α -phase of MoO₃ is promising for detection of NH₃ down to 50 ppb at dry conditions.¹⁸ Moreover, selectivity towards other gases has been achieved by optimizing the sensing temperature.¹⁹ This thermodynamically stable phase²⁰ has been made by reactive sputtering¹⁹ and wet chemistry.²¹⁻²³ Also α -MoO₃ has been made by combustion of sprays²⁴ and evaporation of a Mo source mesh.^{20,25} Depending on flame conditions other crystalline structures (e.g. MoO₂)²⁶ were obtained also. As other phases are not selective to NH₃,²⁷ highly crystalline α -phase is needed. Therefore studying the phase dynamics of polymorphic MoO₃ is important to identify phase transition temperatures and phase stability, as with polymorphic WO₃.²⁸ Knowing the phase dynamics enables tailoring of the thermal treatment and selection of the sensor operational temperature.

Usual operating temperatures of MoO_3 gas sensors are from 250 to 500 °C.^{18,19,22} This necessitates high thermal stability of MoO_3 to prevent
structural alterations during operation and thus enable long-term stability. However, MoO₃ has a low melting temperature (801 °C) which is even lower in the nanoscale where sublimation of particles ($d_{BET} = 40$ nm) was observed already at 790 °C.²⁴ A possible way to stabilize such materials is by addition of foreign oxides and doping that can improve thermal phase stability,^{29,30} inhibit thermal growth of crystal and grain size³¹ and stabilize the particle sintering neck.³² Furthermore, reduced grain and sinter neck size can increase the sensitivity dramatically.^{33,34}

Here, pure and Si-doped MoO_x nanoparticles are made by flame spray pyrolysis (FSP) and directly deposited onto sensor substrates.³⁵ Optimal annealing conditions for synthesis of highly crystalline pure α -MoO₃ are identified by *in-situ* thermally-induced phase dynamics. The effect of Sidoping on the thermal stability of MoO₃ is analyzed with respect to crystal and grain growth and correlated to NH₃ sensitivity and selectivity. Finally, the detection of breath-relevant NH₃ concentrations down to 400 ppb is presented under realistic conditions (90% RH).

2.2 Experimental

2.2.1 Particle and sensor fabrication

Si-doped MoO₃ nanoparticles are made by FSP that is described in more detail elsewhere.³⁶ As dictated by the nominal SiO₂ content (0 -20 wt%), the precursor solution consists of ammonium molybdate tetrahydrate (Aldrich, \geq 99%) and hexamethyldisiloxane (HMDSO, Aldrich, \geq 99%) dissolved in a 1:1 (by volume) mixture of ethylene glycol (Fluka, \geq 99.5%) and ethanol (Fluka, \geq 99.5%) at 0.2 M total metal (Si and Mo) concentration. This solution is supplied at a rate of 5 mL min⁻¹ through the FSP nozzle and dispersed to a fine spray with 5 L min⁻¹ oxygen (pressure drop 1.6 bar). The spray is ignited by a supporting ring-shaped, premixed methane/oxygen flame ($CH_4 = 1.25 \text{ Lmin}^{-1}$, $O_2 = 3.2 \text{ Lmin}^{-1}$). Additional 5 L min⁻¹ sheath oxygen is supplied from an annulus surrounding that flame to ensure excess oxidant flow.

Sensing films are formed by direct deposition³⁵ of the product nanoparticles for 4 min onto a 15 mm x 13 mm x 0.8 mm water-cooled Al₂O₃ sensor substrate (Electronic Design Center, Case Western Reserve University, USA) 20 cm above the FSP nozzle. Nanoparticles that are not deposited onto the substrate are collected onto a water-cooled glass-fiber filter (GF6 Albet-Hahnemuehle, 257 mm diameter) 50 cm above the nozzle with a vacuum pump. The substrates feature a set of interdigitated Pt electrodes (sputtered, 350 µm width and spacing) and a Pt resistance temperature detector (RTD) on the front side with a Pt heater on the back. The sensing films are mechanically stabilized by improving their cohesion and adhesion by *in-situ* annealing:³⁷ lowering the nanoparticle-laden sensing substrates to 15 cm above the nozzle followed by impingement of a spray flame fed with 12 mL min⁻¹ xylene and dispersed by 5 L min⁻¹ oxygen for 30 s. Subsequent annealing of the sensors for 5 h at 450 °C in an oven (Carbolite GmbH, Germany) thermally stabilizes the sensing films and prevents sintering and drift of their signal during sensor operation. Similar conditions are applied to thermal stability investigations of the filtercollected nanoparticles.

2.2.2 Particle characterization

X-ray diffraction (XRD) patterns are obtained by a Bruker, AXS D8 Advance diffractometer operated at 40 kV and 30 mA at 2 θ (Cu K_{α}) = 10 - 60°. For standard, room temperature XRD, the scanning step size and speed are 0.021° and 0.084° s⁻¹, respectively. Crystal phases are identified by comparison to structural parameters of orthorhombic³⁸ α -MoO₃ and monoclinic³⁹ β -MoO₃, Mo₄O₁₁ (PDF 72-0447), and MoO₂.⁴⁰ The corresponding crystal sizes are determined by the Rietveld fundamental parameter method. The lattice parameter alterations are identified with the software Bruker Diffrac.eva V3.1 based on the observed peak shifts.

High temperature (HT) XRD is performed at the above step size but increased scanning speed of 0.161° s⁻¹ to reduce the exposure time. These measurements are carried out in a high temperature chamber (HTK 1200N, Anton Paar, Austria) with a heating and cooling rate of 0.5 °C s⁻¹. The crystalline mass fraction (CMF) of pure MoO_x is obtained by admixing a crystalline, internal standard (NiO, 50 wt%, ~325 mesh, Sigma Aldrich) to the powder.⁴¹ Crystalline NiO (Bunsenite, PDF 47-1049) is selected as standard since its main XRD peaks at 37.2 and 43.3° do not interfere with MoO_x and no interaction during annealing is detected. The CMF of MoO_x is then determined by comparison of the peak area ratio of MoO_x to NiO to a reference ratio with entirely crystalline MoO_x. The reference ratio is defined as the peak area ratio after heat treatment, where complete crystallization of MoO₃ is achieved as evidenced by a straight XRD baseline.

The specific surface area (SSA) is obtained by nitrogen adsorption at 77 K (Micromeritics II Plus) with the Brunauer-Emmett-Teller (BET) method. Prior to BET measurement, samples are degassed under vacuum for 1 h. Equivalent diameters are calculated assuming a spherical geometry and the densities of α -MoO₃ (4.71 g cm⁻³) and amorphous SiO₂ (2.19 g cm⁻³) according to nominal composition. Transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) are conducted with a Tecnai F30 ST (FEI, FEG) operated at 300 kV. STEM images are obtained with a high-angle annular dark field (HAADF) detector with bright Z contrast. Energy dispersive X-ray spectroscopy (EDXS) is performed with an attached EDAX detector. The analyzed particles are dispersed in ethanol and deposited onto copper grid supported and perforated carbon foils.

2.2.3 Sensor characterization

The morphology of the sensing film is investigated by scanning electron microscopy (SEM) with a Hitachi FE-SEM 4000 operated at 3 kV. Figure 2.1a shows the experimental set-up for sensor characterization. Analyzed gas samples are prepared by first mixing dry and humidified synthetic air (Pan Gas 5.0, C_nH_m and $NO_x \le 100$ ppb) to achieve the desired relative humidity (RH) levels. Humidified air is produced by bubbling synthetic dry air through distilled water that is maintained at 20 °C to avoid condensation in the piping.¹⁶



Figure 2.1: (a) Schematic of experimental set-up for sensor evaluation: The analyte gases and relative humidity (RH) are dosed and admixed by calibrated mass flow controllers (MFC). The MoO_3 -based sensors are mounted on a Macor holder and placed in a T-shaped chamber⁴³. A DC power source heats the sensor to set operational temperature. The film resistance (R_f) is measured by a picoammeter. (b) Electric equivalent circuit for NH_3 detection.

The RH of the generated gas mixture is continuously monitored by a sensor (SHT2x, Sensirion AG). Analyte gases, i.e. NH₃ (10 ppm in N₂, Pan Gas 5.0), acetone (10 ppm in synthetic air, Pan Gas 5.0), NO (10 ppm in N₂, Pan Gas 5.0) and CO (0.1010 mol% in N_2 , Pan Gas 5.0), are admixed then by calibrated mass flow controllers (Bronkhorst, Netherlands). Stainless steel static mixers ensure a homogeneous mixing. To prevent analyte adsorption on the inner piping surface, solely Teflon[®] tubes are used. Additionally for tests with RH, the piping is heated⁴² to ~50 °C to avoid water condensation and subsequent analyte absorption into the water film. The Si-doped (0 - 20 wt%) MoO₃ sensors are installed inside a T-shaped chamber.⁴³ The ohmic film resistance (R_f) between the interdigitated electrodes is determined with a picoammeter (Keithley, 6487, USA) as illustrated by the electric equivalent circuit (Figure 2.1b). In series measured parasitic holder (R_h) and wire resistances (R_w) are negligible (< 1 Ω) and much lower than $R_f (10^7 - 10^8 \Omega)$. The heating power is supplied by a DC source (Agilent, E3644A, USA). Sensors are operated between 350 to 425 °C and monitored by the embedded RTD. The sensor response S is defined as:¹⁶

$$S = \frac{R_{air}}{R_{analyte}} - 1 \tag{1}$$

where R_{air} is the film resistance in air at given RH and $R_{analyte}$ is that resistance at a given analyte concentration (NH₃, acetone, CO, NO) in air. The cross-sensitivity to humidity (CS) is defined as:¹⁶

$$CS = \left| \frac{S_{dry} - S_{RH}}{S_{dry}} \right| \tag{2}$$

where S_{dry} and S_{RH} are the sensor responses in dry air and at given RH, respectively. The sensor response time is the time needed to reach 90% of

the response resistance change to 1000 ppb NH₃. Recovery time is the time to recover 90% of the response resistance change to that of 1000 ppb NH₃.

2.3 Results and discussion

2.3.1 Particle characterization and MoO_x phase dynamics

Figure 2.2a shows the XRD patterns of as-prepared flame-made pure and Si-doped MoO_x nanoparticles. Pure MoO_x (black pattern) consists of thermodynamically stable α -MoO₃ (triangles), β -MoO₃ (squares), MoO₂ (circles) and Mo₄O₁₁ (diamonds). A large hump from 20 to 36° indicates amorphous MoO_x. The formation of metastable β -MoO₃, Mo₄O₁₁, MoO₂ and amorphous MoO_x is attributed to the high quenching rates of FSP.⁴⁴ Doping with increasing Si content gradually reduces both α - and β -MoO₃ and at 20 wt% SiO₂ (turquois pattern) these phases have been suppressed totally in favor of MoO₂ and Mo₄O₁₁. The hump at 20 to 36° is enlarged for Si-doped MoO_x indicating the additional formation of amorphous SiO₂.

Since high degree of crystallinity, pure α -MoO₃²² and phase stability are required for improved NH₃ selectivity by the sensor, the MoO_x phase dynamics during annealing are investigated by *in-situ* XRD. Figure 2.2b shows the XRD patterns of pure MoO_x (Figure 2.2a, black pattern) when heated up to 500 °C (red patterns) and cooled down to room temperature (blue patterns). Between 25 and 200 °C, no notable change is visible. At 250 °C, peaks at 23°, 25°, 27.3° and 33.7° emerge indicating formation of β- and some α -MoO₃. These phases are formed by crystallization of amorphous MoO_x based on the calculated CMF of MoO_x that increases from around 30 to 65 wt%. The formation of β-MoO₃ at this temperature is in agreement with *in-situ* Raman studies on amorphous MoO_x.⁴⁵



Figure 2.2: XRD patterns of pure and Si-doped MoO_x powders: (a) as-prepared consists of α -MoO₃ (triangles), β -MoO₃ (squares), MoO₂ (circles) and Mo₄O₁₁ (diamonds). (b) In-situ XRD phase dynamic of as-prepared pure MoO_x during heat-up to 500 °C (red patterns) and cool-down to room temperature (blue patterns). Note that NiO (50 wt%) is added just for this experiment as internal standard to determine the crystalline mass fraction (CMF) of MoO_x. (c) Annealed at 450 °C for 5 h in dry air and all becoming solely α -MoO₃. The Si-doping does not affect crystal composition but the (040) peak is slightly reduced and shifted (inset) as observed also for the (021) peak compared to pure MoO₃ (black pattern).

At 300 °C, crystalline β -MoO₃ peaks decrease in height and broaden indicating reduced crystal size while those of α -MoO₃ are preserved. This is attributed to a possible thermally-induced recrystallization of the β -phase since at 350 °C again β -MoO₃ peaks increase. The more pronounced peak at 27.3° indicates additional formation of α -MoO₃ at 350 °C. Furthermore, a transition from β - to α -phase takes place in agreement to literature⁴⁵ which is completed here at 400 °C with an α -MoO₃ CMF above 90 wt%.

Most notably α -MoO₃ is stable to 500 °C and preserved during cooldown to 25 °C consistent with MoO₃ nanoribbons⁴⁶ where the α -MoO₃ stability was demonstrated up to 600 °C. Also during a subsequent and identical annealing cycle (not shown here), the pure α -MoO₃ is preserved, confirming its thermal stability. The peak shift of (0b0) planes of the α phase (where b = 2, 4, 6 as denoted in Figure 2.2b) with increasing temperature is attributed to thermal expansion in the <0b0> direction.⁴⁷ The lattice parameter b represents the interatomic distance between the stacked layers of MoO₆ octahedra.⁴⁸ The phase dynamics of Si-doped MoO₃ are similar to those of Figure 2.2b. However, the Si-doping retards the final transition to α -MoO₃ that is completed at 450 °C.

So annealing at 450 °C for 5 h is selected for pure and Si-doped MoO_3 to ensure sufficient stability for selective sensing of NH_3 . As expected, pure

 α -MoO₃ is obtained for all samples at these conditions (Figure 2.2c). For Sidoped MoO₃, the (040) peak is slightly lower and wider than for pure MoO₃. As indicated by the magnified XRD pattern section (Figure 2.2c, inset), the (040) and (021) peaks of pure MoO₃ at $2\theta = 25.705^{\circ}$ and 27.335°, respectively, are slightly shifted to 25.670° and 27.290° for Si-doped MoO₃ while no shift is observed for their (110) peak. This corresponds to a lattice parameter expansion in the b-axis from 13.858 to 13.871 Å and in the c-axis from 3.697 to 3.701 Å. This could indicate the formation of interstitial solid solutions by incorporation of Si⁴⁺ into the orthorhombic MoO₃ lattice. In fact, the ionic radius⁴⁹ of Si⁴⁺ (40 pm) is considerably smaller than Mo⁶⁺ (59 pm), thus interstitial incorporation of Si into the MoO₃ lattice is possible, as observed⁵⁰ for aerosol-made Si-doped TiO₂. Formation of these interstitial solid solutions could take place during FSP since mixing happens on a molecular level enabling sufficiently fast incorporation⁵¹ even though residence times at high temperatures are short.⁴⁴ It should be noted that Vegard's law⁵² does not apply in the investigated Si range as crystal size (Figure 2.3, triangles) is rather constant and the (040) and (021) peaks do not shift further above 1.5 wt% SiO₂ (Figure 2.2c, inset). This indicates⁵³ that the solubility of Si⁴⁺ in MoO₃ might be exceeded already at 1.5 wt% SiO₂. Figure 2.3 shows average particle (d_{BET} , circles) and crystal (d_{XRD} , triangles) sizes of as-prepared and annealed particles as a function of SiO_2 content. The d_{BET} of as-prepared powder (filled circles) increases from 9.6 to 11.1 nm for 0 to 20 wt% SiO₂, indicating increased extend of necking and aggregation. The nanostructured morphology and fine crystallinity of pure MoO₃ were confirmed by TEM (Figure 2.3a) and electron diffraction (ED) patterns (Figure 2.3b), respectively. Individual crystal sizes for as-prepared powder are not calculated from the XRD patterns (Figure 2.2a) since peaks of the multiple MoO_x phases are overlapping, making a crystal size extraction unreliable.

2.3.2 Thermal stabilization

By annealing at 450 °C for 5 h, pure MoO_x particles grow to ribbonlike structures (Figure 2.3d) with large crystallites, as indicated by XRD (triangles) and BET (open circles) and confirmed by bright spots in ED patterns (Figure 2.3c). The difference between average crystal and BET particle size indicates elongated particle shape, polycrystallinity and/or necking. Doping with Si reduces particle and crystal growth significantly. Already at 1.5 wt% SiO₂ content, the crystal size (d_{XRD}) is decreased to 65 from 147 nm (pure MoO₃) while the particle size (d_{BET}) is reduced even more to 83 from 272 nm (pure MoO₃), demonstrating the superior thermal stability of Si-doped MoO₃. Interesting enough, the crystal size does not decrease further at higher dopant level and remains rather constant (Figure 2.3, triangles), similarly for all miller indices denoted in Figure 2.2c. This is consistent with the observed peak shift (Figure 2.2c, inset) suggesting that a solid solution is formed that thermally stabilizes the crystal size.

Excess Si that is not incorporated into the orthorombic MoO₃ lattice forms domains of SiO₂, as supported by TEM images of MoO₃ doped with 3 wt% SiO₂ (Figure 2.4a) showing segregated, amorphous SiO₂ at the edges of MoO₃ particles and sinter necks, similar to Si-doping of SnO₂ sensors[Ref. 32, Figure 7]. That way, MoO₃ sinter necks are narrowed and sintering rates reduced, so formation of large MoO₃ crystals is inhibited as with Si-doped TiO₂⁵⁰ and WO₃.³⁰ Larger domains of SiO₂ are formed when increasing the dopant level to 5 wt% SiO₂, as shown in Figure 2.4b.



Figure 2.3: Average particle (d_{BET} , circles) and crystal sizes (d_{XRD} , triangles) as function of SiO₂ content for as-prepared (filled symbols) and annealed (open symbols) powders at 450 °C for 5 h. As-prepared powder consists of nanostructured particles with ultrafine crystallinity, as confirmed by TEM (a) and ED patterns (b) for pure MoO_x . During annealing, particles grow to large, ribbon-like MoO_3 structures (d) with large crystallites, as indicated by XRD and bright spots in ED pattern (c). Doping with Si strongly reduces the particle and crystal sizes.

EDX analysis was performed to analyze the local atomic composition. So selected areas of segregated SiO₂ (Figure 2.4d) and MoO₃ particles (Figure 2.4c) were analyzed, as marked by white squares in the STEM inset of Figure 2.4b. Indeed, MoO₃ particles consist primarily of Mo and O (Figure 2.4c) while Si is below the detection limit suggesting that any Si atoms present are incorporated interstitially. On the other hand, domains of segregated SiO₂ (Figure 2.4d) consist primarily of Si and O with only minor Mo atoms. These results are consistent to XRD and TEM analysis. At 20 wt% SiO₂ (Figure 2.4e), large domains of segregated SiO₂ were formed



that completely separated the MoO_3 grains similar to SnO_2 at these Sidoping levels.³²

Figure 2.4: TEM of (a) 3 wt% Si-doped MoO_3 after annealing indicates segregated amorphous SiO_2 at the MoO_3 particle surface and sinter necks. These amorphous domains increase in size at higher SiO_2 content, e.g. at 5 wt% (b). Corresponding STEM and EDX analysis for selected areas (white squares at inset) confirm that MoO_3 particles consist primarily of Mo and O atoms (c) while mainly Si and O and minor Mo are found in domains of segregated SiO_2 (d). In both analyses, C and Cu peaks are traced to the applied substrate. (e) At 20 wt% Si-doping, MoO_3 grains are completely separated by domains of insulating SiO_2 .

The morphology of directly deposited pure and Si-doped MoO₃ nanoparticles onto sensor substrates was investigated also by SEM. After annealing, pure MoO₃ films or layers are formed on the substrate (Figure 2.5a) consisting of thin belts (or platelets, ribbons, disks) with dimensions and shape comparable to those collected from the filter and similarly annealed (Figure 2.3d). Such morphology was also obtained for MoO₃ grown on Al₂O₃²⁵ and Si²⁰ substrates. Doping with Si, however, dramatically alters the deposited film structure (Figure 2.5b). In fact, already at 3 wt% SiO₂ content, a significantly finer network with increased porosity is visible. These structures consist of agglomerated nanoparticles similar to filter-collected and annealed ones (Figure 2.4a). Furthermore, longer, needle-like structures are created with axial dimensions of several µm but significantly reduced lateral dimensions compared to pure MoO₃ (Figure 2.5a).



Figure 2.5: SEM image (top view) of pure (a) and 3 wt% Si-doped (b) MoO_3 films after annealing at 450 °C for 5 h. Pure MoO_3 has grown to thin belts (platelets, ribbons or disks) with dimensions of several μm (a). The Si-doping alters drastically that morphology to increased porosity (b) by a finer network consisting of agglomerated nanoparticles and needle-like structures (inset).

2.3.3 Sensor performance in dry air

Figure 2.6a shows the response of pure and Si-doped MoO₃ sensors to 1000 ppb NH₃ (triangles), acetone (circles), NO (squares) and CO (diamonds) in dry air at 400 °C. NH₃ interacts with α -MoO₃ resulting in a sensor response of 0.22. Doping MoO₃ with Si enhances this sensitivity despite Si being inert and not actively contributing to analyte detection. By increasing the SiO₂ content from 0 to 3 wt%, the NH₃ response almost triples to 0.53.

Adding small amounts (< 1.5% SiO₂) of Si slightly increases the sensitivity of NH_3 (Figure 2.6a) attributed³³ to the drastic crystal size reduction (Figure 2.3) of MoO₃ by formation of solid solution as indicated by the shift of its XRD reflection (Figure 2.2c, inset) and the corresponding change in lattice parameters. Beyond 1.5 wt% SiO₂, no changes on lattice and crystal sizes occur but the reduced sinter neck size of the MoO_3 structures by the additional segregated SiO₂ (Figure 2.4a for 3 wt%) should narrow the conduction channel locally, as indicated also by the increasing film resistance (Figure 2.6a, inset). This contributes to improved NH₃ sensitivity as observed from 1.5 to 3 wt% SiO₂ (Figure 2.6a), similar to Sidoped SnO₂ [Ref. 32 Figure 9]. Narrowing of these sinter necks (to sizes approaching the extension of the surface charge region 33,54) leads to increasing electron depletion of the conduction channel. So during exposure to the analyte gas (here NH_3), enhanced electron "injection" takes place³⁴. Consequently, charge carrier mobility and thus film resistance are dominated by surface phenomena instead of bulk properties leading to increased sensor sensitivity to the analyte, as observed also for sintered porous SnO₂ gas sensors³³. Also the altered film morphology from thin beltlike (Figure 2.5a) to nanoparticle/needle-like (Figure 2.5b) favors gas sensing due to the higher surface-to-volume ratio of the latter.¹⁵



Figure 2.6: (a) Average sensor response as a function of SiO_2 content to 1000 ppb ammonia (triangles), acetone (circles), NO (squares) and CO (diamonds) in dry air at 400 °C. The baseline film resistance increases with increasing SiO_2 content (inset). Error bars indicate the response variability to at least two identical consecutive analyte exposures. Most such bars are smaller than the data symbols. (b) Response of optimally Si-doped (3 wt%) MoO₃ sensor as a function of operational temperature. The response and recovery times to 1000 ppb of ammonia (inset) decrease continuously with increasing sensor temperature.

Above 3 and up to 20 wt% SiO₂ content, the sensitivity progressively deteriorates. This is attributed to formation of large and inert SiO₂ domains (Figure 2.4e), that eventually isolate the sensitive MoO₃ crystallites and turn the sensor into an insulator, similar to Si-doped SnO_2^{32} and WO₃.³⁰ This observation is also supported by the continuously increasing baseline film resistance (Figure 2.6a, inset) with increasing SiO₂ content.

The Si-doping improves also the NH₃ selectivity towards other interfering gases present in human breath (Figure 2.6a). At 3 wt% SiO₂, an optimum is reached with a response ratio to acetone (S_{NH3} / S_A) of 3.6 and to NO of 7.9. No sensitivity is observed for CO similar to sputtered α -MoO₃ films.¹⁹ The present Si-doped MoO₃ (3 wt%) sensors have higher response (0.53) than sol-gel made MoO₃ films (~0.18)¹⁸ and superior selectivity towards NO and CO.²² Furthermore, response and recovery times of 3.6 and 7 min at 400 °C (Figure 2.6b, inset) are comparable¹⁸ even though the sensors are operated here at lower temperature.

The operating temperature of the sensor is investigated from 350 to 425 °C with respect to NH₃ response and selectivity using the optimally Sidoped (3 wt%) MoO₃ sensor (Figure 2.6b). With increasing temperature, the response to NH₃ increases reaching a maximum at 400 °C. In contrast, the response to interfering acetone decreases. This is probably attributed to combustion of acetone in the upper film layer, as with Si-doped WO₃.¹⁶ The corresponding selectivity to NH₃ is maximal at 400 °C. So that temperature is selected as the operational one for further testing due to the improved NH₃ response and selectivity. These results are consistent with sputtered MoO₃ films where optimum NH₃ response and selectivity had been reported at 425 °C.¹⁹

2.3.4 Sensor performance in humid air

The RH in the breath is 89 - 97%¹⁴ making the assessment of these sensors under more realistic conditions crucial. So an optimally Si-doped sensor (3 wt%) operated at 400 °C is tested for detection of low ammonia concentrations down to 400 ppb at 90% RH (Figure 2.7) corresponding to the lower limit of healthy people.⁵ RH changes the sensor baseline resistance slightly from 23.8 M Ω (Figure 2.6a, inset) to 26.4 M Ω which is comparable to Si-doped WO₃ at these temperatures.¹⁶



Figure 2.7: The film resistance of the optimally Si-doped (3 wt% SiO₂) 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.

When exposed to 1000 ppb of NH₃, the film resistance decreases to 24.9 M Ω with a sensor response time of 50 s, resulting in a response of 0.06. This corresponds to a CS of 89%. Similar reduction of sensor response has been observed already for other metal-oxides such as SnO₂⁵⁵ or WO₃.¹⁶ The baseline is fully recovered within 60 s. Most notably, NH₃ levels down to

400 ppb are detected with high signal-to-noise ratio (> 15) that can be clearly distinguished from other concentrations (700 and 1000 ppb) following a nearly linear ($R^2 = 0.992$) calibration (Figure 2.7, inset). The demonstrated NH₃ response of these flame-made sensors under realistic breath conditions (90% RH) is an important step towards ESRD detection since the tested NH₃ levels correspond to the lower limit of concentrations present in exhaled human breath of ESRD patients.⁵ In addition, this sensor has the potential to real-time monitor dialysis therapy due to its fast response and recovery times and high NH₃ resolution.

2.4 Conclusions

Pure and Si-doped MoO_x nanoparticles of about 10 nm in grain size were made by flame spray pyrolysis (FSP) and directly deposited onto sensor substrates. The MoO_x phase dynamics were investigated *in-situ* by XRD from 25 to 500 °C. Between 300 - 350 °C a thermally-induced recrystallization of β -MoO₃ was observed for pure and Si-doped MoO_x, respectively. An optimal annealing temperature for synthesis of highly crystalline α -MoO₃ was identified at 450 °C. Addition of SiO₂ (1.5 - 20 wt%) significantly enhanced the thermal stability of the sensor by apparent incorporation of Si⁴⁺ into the MoO₃ lattice and formation of segregated, amorphous SiO₂. This prevented MoO₃ crystal and grain growth and altered the macroscopic morphology of the sensing film from belt- (or platelet- or disk-) to finer nanoparticle/needle-like.

 MoO_3 sensors doped with 1.5 - 3.5 wt% SiO_2 showed enhanced response and superior selectivity for NH_3 towards other breath-relevant gases (acetone, NO, CO) than pure MoO_3 . Optimal dopant level and sensor operational temperature were identified at 3 wt% SiO_2 and 400 °C, respectively. This sensor could clearly distinguish breath-relevant NH_3 levels down to 400 ppb at realistic conditions (90% RH) with fast response and recovery times (< 1 min) and operational stability. Such sensors can be readily incorporated into portable devices, so they have high potential for further development towards a simple hand-held breath NH_3 detector for early-stage renal disease (ESRD) detection and monitoring of haemodialysis.

2.5 References

- [1] ESRD Patients in 2012: A Global Perspective, Fresenius Medical Care, Bad Homburg, 2013.
- F. Valderrábano, R. Jofre and J. M. López-Gómez, Quality of life in end-stage renal disease patients, *Am. J. Kidney Dis.*, 2001, 38, 443-464.
- [3] U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.
- [4] L. R. Narasimhan, W. Goodman and C. K. N. Patel, Correlation of breath ammonia with blood urea nitrogen and creatinine during hemodialysis, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, 98, 4617-4621.
- [5] S. Davies, P. Spanel and D. Smith, Quantitative analysis of ammonia on the breath of patients in end-stage renal failure, *Kidney Int.*, 1997, 52, 223-228.
- [6] M. Z. Dai, Y. L. Lin, H. C. Lin, H. W. Zan, K. T. Chang, H. F. Meng, J. W. Liao, M. J. Tsai and H. Cheng, Highly Sensitive Ammonia Sensor with Organic Vertical Nanojunctions for Noninvasive Detection of Hepatic Injury, *Anal. Chem.*, 2013, 85, 3110-3117.
- [7] T. Hibbard, K. Crowley, F. Kelly, F. Ward, J. Holian, A. Watson and A. J. Killard, Point of Care Monitoring of Hemodialysis Patients with

a Breath Ammonia Measurement Device Based on Printed Polyaniline Nanoparticle Sensors, *Anal. Chem.*, **2013**, 85, 12158-12165.

- [8] Z. H. Endre, J. W. Pickering, M. K. Storer, W. P. Hu, K. T. Moorhead, R. Allardyce, D. O. McGregor and J. M. Scotter, Breath ammonia and trimethylamine allow real-time monitoring of haemodialysis efficacy, *Physiol. Meas.*, 2011, 32, 115-130.
- [9] D. Smith, T. Wang, A. Pysanenko and P. Španěl, A selected ion flow tube mass spectrometry study of ammonia in mouth- and nose-exhaled breath and in the oral cavity, *Rapid Commun. Mass Spectrom.*, 2008, 22, 783-789.
- [10] S. J. Davies, P. Španěl and D. Smith, Breath analysis of ammonia, volatile organic compounds and deuterated water vapor in chronic kidney disease and during dialysis, *Bioanalysis*, **2014**, 6, 843-857.
- [11] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, J. Breath Res., 2015, 9, 047101.
- [12] T. Hibbard and A. J. Killard, Breath ammonia levels in a normal human population study as determined by photoacoustic laser spectroscopy, *J. Breath Res.*, **2011**, 5, 037101.
- [13] M. Phillips, J. Herrera, S. Krishnan, M. Zain, J. Greenberg and R. N. Cataneo, Variation in volatile organic compounds in the breath of normal humans, J. Chromatogr. B. Biomed. Appl., 1999, 729, 75-88.
- [14] L. Ferrus, H. Guenard, G. Vardon and P. Varene, Respiratory water loss, *Respir. Physiol.*, **1980**, 39, 367-381.
- [15] M. Righettoni, A. Amann and S. E. Pratsinis, Breath analysis by nanostructured metal oxides as chemo-resistive gas sensors, *Mater. Today*, 2015, 18, 163-171.
- [16] M. Righettoni, A. Tricoli and S. E. Pratsinis, Si:WO₃ Sensors for Highly Selective Detection of Acetone for Easy Diagnosis of Diabetes by Breath Analysis, *Anal. Chem.*, **2010**, 82, 3581-3587.

- [17] M. Righettoni, A. Schmid, A. Amann and S. E. Pratsinis, Correlations between blood glucose and breath components from portable gas sensors and PTR-TOF-MS, *J. Breath Res.*, 2013, 7, 037110.
- [18] P. Gouma, K. Kalyanasundaram, Y. Xiao, M. Stanacevic and L. Wang, Nanosensor and Breath Analyzer for Ammonia Detection in Exhaled Human Breath, *Sensors Journal, IEEE*, **2010**, 10, 49-53.
- [19] D. Mutschall, K. Holzner and E. Obermeier, Sputtered molybdenum oxide thin films for NH₃ detection, *Sens. Actuators B*, **1996**, 36, 320-324.
- [20] L. Cai, P. M. Rao and X. Zheng, Morphology-Controlled Flame Synthesis of Single, Branched, and Flower-like α-MoO₃ Nanobelt Arrays, *Nano Lett.*, **2011**, 11, 872-877.
- [21] X. W. Lou and H. C. Zeng, Hydrothermal Synthesis of α-MoO₃ Nanorods via Acidification of Ammonium Heptamolybdate Tetrahydrate, *Chem. Mater.*, **2002**, 14, 4781-4789.
- [22] A. K. Prasad, D. J. Kubinski and P. I. Gouma, Comparison of sol-gel and ion beam deposited MoO₃ thin film gas sensors for selective ammonia detection, *Sens. Actuators B*, **2003**, 93, 25-30.
- [23] G. R. Patzke, A. Michailovski, F. Krumeich, R. Nesper, J.-D. Grunwaldt and A. Baiker, One-Step Synthesis of Submicrometer Fibers of MoO₃, *Chem. Mater.*, 2004, 16, 1126-1134.
- [24] J. A. Azurdia, A. McCrum and R. M. Laine, Systematic synthesis of mixed-metal oxides in NiO-Co₃O₄, NiO-MoO₃, and NiO-CuO systems via liquid-feed flame spray pyrolysis, *J. Mater. Chem.*, 2008, 18, 3249-3258.
- [25] E. Comini, L. Yubao, Y. Brando and G. Sberveglieri, Gas sensing properties of MoO₃ nanorods to CO and CH₃OH, *Chem. Phys. Lett.*, 2005, 407, 368-371.

- [26] W. Merchan-Merchan, A. V. Saveliev and M. Desai, Volumetric flame synthesis of well-defined molybdenum oxide nanocrystals, *Nanotechnology*, 2009, 20, 475601.
- [27] P. Gouma, A. Prasad and S. Stanacevic, A selective nanosensor device for exhaled breath analysis, *J. Breath Res.*, **2011**, 5, 037110.
- [28] M. Righettoni and S. E. Pratsinis, Annealing dynamics of WO₃ by in situ XRD, *Mater. Res. Bull.*, 2014, 59, 199-204.
- [29] L. Wang, A. Teleki, S. E. Pratsinis and P. I. Gouma, Ferroelectric WO₃ Nanoparticles for Acetone Selective Detection, *Chem. Mater.*, 2008, 20, 4794-4796.
- [30] M. Righettoni, A. Tricoli and S. E. Pratsinis, Thermally Stable, Silica-Doped ε-WO₃ for Sensing of Acetone in the Human Breath, *Chem. Mater.*, 2010, 22, 3152-3157.
- [31] C. Xu, J. Tamaki, N. Miura and N. Yamazoe, Stabilization of SnO₂ ultrafine particles by additives, *J. Mater. Sci.*, **1992**, 27, 963-971.
- [32] A. Tricoli, M. Graf and S. E. Pratsinis, Optimal Doping for Enhanced SnO₂ Sensitivity and Thermal Stability, *Adv. Funct. Mater.*, 2008, 18, 1969-1976.
- [33] C. Xu, J. Tamaki, N. Miura and N. Yamazoe, Grain size effects on gas sensitivity of porous SnO₂-based elements, *Sens. Actuators B*, **1991**, 3, 147-155.
- [34] N. Barsan and U. Weimar, Conduction Model of Metal Oxide Gas Sensors, J. Electroceram., 2001, 7, 143-167.
- [35] L. M\u00e4dler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, *Sens. Actuators B*, **2006**, 114, 283-295.
- [36] L. Mädler, W. J. Stark and S. E. Pratsinis, Flame-made Ceria Nanoparticles, *J. Mater. Res*, **2002**, 17, 1356-1362.

- [37] A. Tricoli, M. Graf, F. Mayer, S. Kühne, A. Hierlemann and S. E. Pratsinis, Micropatterning Layers by Flame Aerosol Deposition-Annealing, *Adv. Mater.*, 2008, 20, 3005-3010.
- [38] H. E. Swanson, R. K. Fuyat and G. M. Ugrinic, Standard X-ray diffraction powder patterns. III. Data for 34 inorganic substances, *Circ. Natl. Bur. Stand.*, 1954, C539, 1-73.
- [39] J. B. Parise, E. M. McCarron III, R. Von Dreele and J. A. Goldstone, β-MoO₃ produced from a novel freeze drying route, J. Solid State Chem., 1991, 93, 193-201.
- [40] M. Ghedira, C. Dodinh, M. Marezio and J. Mercier, The Crystal Structure of Mo_{0.975}Ti_{0.025}O₂ between 24 and 900°C, *J. Solid State Chem.*, **1985**, 59, 159-167.
- [41] B. Ohtani, Y. Ogawa and S.-i. Nishimoto, Photocatalytic Activity of Amorphous–Anatase Mixture of Titanium(IV) Oxide Particles Suspended in Aqueous Solutions, J. Phys. Chem. B, 1997, 101, 3746-3752.
- [42] S. F. Solga, M. Mudalel, L. A. Spacek, R. Lewicki, F. Tittel, C. Loccioni, A. Russo and T. H. Risby, Factors influencing breath ammonia determination, J. Breath Res., 2013, 7, 037101.
- [43] M. Righettoni, A. Tricoli, S. Gass, A. Schmid, A. Amann and S. E. Pratsinis, Breath acetone monitoring by portable Si:WO₃ gas sensors, *Anal. Chim. Acta*, 2012, 738, 69-75.
- [44] R. Strobel, M. Maciejewski, S. E. Pratsinis and A. Baiker, Unprecedented formation of metastable monoclinic BaCO₃ nanoparticles, *Thermochim. Acta*, 2006, 445, 23-26.
- [45] D. E. Diaz-Droguett, R. El Far, V. M. Fuenzalida and A. L. Cabrera, In situ-Raman studies on thermally induced structural changes of porous MoO₃ prepared in vapor phase under He and H₂, *Mater. Chem. Phys.*, **2012**, 134, 631-638.

- [46] J. V. Silveira, L. L. Vieira, J. Mendes Filho, A. J. C. Sampaio, O. L. Alves and A. G. Souza Filho, Temperature-dependent Raman spectroscopy study in MoO₃ nanoribbons, *J. Raman Spectrosc.*, 2012, 43, 1407-1412.
- [47] T. Leisegang, A. A. Levin, J. Walter and D. C. Meyer, In situ X-ray analysis of MoO₃ reduction, *Cryst. Res. Technol.*, **2005**, 40, 95-105.
- [48] P. Badica, Preparation through the Vapor Transport and Growth Mechanism of the First-Order Hierarchical Structures of MoO₃ Belts on Sillimanite Fibers, *Cryst. Growth Des.*, 2007, 7, 794-801.
- [49] N. N. Greenwood and A. Earnshaw, *Chemistry of the elements*, Butterworth-Heinemann, Oxford 2nd edn., 1997.
- [50] M. K. Akhtar, S. E. Pratsinis and S. V. R. Mastrangelo, Dopants in Vapor-Phase Synthesis of Titania Powders, J. Am. Ceram. Soc., 1992, 75, 3408-3416.
- [51] D. J. DiGiovanni, T. F. Morse and J. W. Cipolla, Theoretical Model of Phosphorus Incorporation in Silica in Modified Chemical Vapor Deposition, J. Am. Ceram. Soc., 1988, 71, 914-923.
- [52] A. R. Denton and N. W. Ashcroft, Vegard's law, *Physical Review A*, 1991, 43, 3161-3164.
- [53] R. A. Slepetys and P. A. Vaughan, Solid solution of aluminum oxide in rutile titanium dioxide, *J. Phys. Chem.*, **1969**, 73, 2157-2162.
- [54] H. Ogawa, M. Nishikawa and A. Abe, Hall measurement studies and an electrical conduction model of tin oxide ultrafine particle films, J. *Appl. Phys.*, **1982**, 53, 4448-4455.
- [55] A. Tricoli, M. Righettoni and S. E. Pratsinis, Minimal cross-sensitivity to humidity during ethanol detection by SnO₂-TiO₂ solid solutions, *Nanotechnology*, **2009**, 20, 315502.

3

Selective sensing of isoprene by Ti-doped ZnO for breath diagnostics

Abstract Exhaled isoprene could enable non-invasive monitoring of cholesterol-lowering therapies. Here, we report an *isoprene-selective* sensor at high relative humidity (RH) for the first time (to our knowledge). It is made of nanostructured, chemoresistive Ti-doped ZnO particles (10 - 20 nm crystal size) produced by flame spray pyrolysis (FSP) and directly deposited in *one step* onto compact sensor substrates forming highly porous films. 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. These Ti⁴⁺ point defects strongly enhance 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 Ti⁴⁺ 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, NH₃ 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. As a result, an inexpensive isoprene detector has been developed that could be easily incorporated into a portable breath analyzer for non-invasive monitoring of metabolic disorders (e.g. cholesterol).

*published in part in *J. Mater. Chem. B*, **2016**, 4, 5358-5366 and highlighted on that issue's *Cover Page*.

3.1 Introduction

Approximately 39% of the world population has high blood cholesterol that might be responsible for a third of ischaemic heart diseases and strokes leading to over 2.6 million estimated deaths per year.¹ Breath isoprene detection could provide a non-invasive method for easy and rapid assessment of high blood cholesterol synthesis rates and enable real-time monitoring of its therapy.² In fact, the exhaled isoprene excretion in humans is decreased when treated with cholesterol-lowering lova-³ and atorvastatins.⁴ While healthy adults exhale isoprene concentrations typically in the range of 22 to 234 ppb,⁵ altered levels occur also in end-stage renal disease,⁶ lung cancer,⁷ liver disease patients with advanced fibrosis⁸ and during physical activity⁴ indicating the potential of this breath marker.

Several methods have demonstrated high sensitivity, low limit of detection and sufficient selectivity for breath isoprene detection, including selective ion flow tube mass spectrometry (SIFT-MS)⁵ or proton transfer reaction mass spectrometry (PTR-MS).⁴ However, such devices are hardly applicable for daily use in widespread populations, as they are rather expensive with limited portability. In this respect, chemoresistive gas sensors based on nanostructured metal-oxides are rather promising⁹ due to their low fabrication cost, simple applicability and compact size¹⁰ that can be easily integrated into a portable breath sampler.¹¹ However for isoprene, no suitable materials are available that possess sufficiently low detection limit at breath-realistic, high relative humidity (RH, ~89 - 97%)¹² and selectivity against other breath compounds (e.g. NH₃ and acetone).

This need stimulates the exploration of novel materials and concepts. Indeed, *analyte-selectivity* can be found in unprecedented material compositions leading to novel phases, solid solutions and mixed oxides. This has been demonstrated with Cr-doped ε -WO₃ (acetone)¹³ and Si-doped α -MoO₃ (NH₃).¹⁴ Furthermore, the selectivity issue of singular sensors can be overcome by combining differently-doped SnO₂ sensors with individual selectivity to an array (electronic nose) as shown for formaldehyde, a potential tracer for lung cancer and indoor air pollution.¹⁵ Such sensors have been applied already for breath analysis with humans revealing promising correlations with blood glucose levels, especially after overnight fasting.¹⁶

Here, we present for the first time (to our knowledge) an *isoprene-selective* chemoresistive sensor consisting of Ti-doped ZnO. These nanostructured particles are made by flame spray pyrolysis (FSP) and directly deposited onto sensor substrates. Besides sensing, such transitional metal doped ZnO are attractive as transparent conductors¹⁷ and can feature ferromagnetism at room temperature,^{18,19} that is promising for spintronics.²⁰ Here, studying the Ti incorporation mechanism at the ZnO lattice and the surface interactions with the analyte reveal the apparent unique role of Ti⁴⁺ cations for selective isoprene detection. An optimum Ti content is identified with respect to isoprene sensitivity and selectivity enabling the detection of ultra-low isoprene concentrations down to *5 ppb* at breath-realistic conditions (90% RH). The developed sensor could facilitate easy monitoring of daily blood cholesterol levels for better treatment and reduced associated risks.

3.2 Experimental

3.2.1 Particle and sensing film production

Ti-doped ZnO nanoparticles are produced in a FSP reactor (Figure 3.1a) elaborated elsewhere.²¹ The FSP precursor solution consists of zinc 2ethylhexanoate (Strem chemicals, purity > 99%, 22 wt% Zn) and titanium tetraisopropoxide (TTIP, Sigma Aldrich, purity > 97.0%) diluted in xylene (Sigma Aldrich, purity $\ge 96\%$). The composition is varied to obtain different Ti contents (0 - 100 mol%) while keeping an overall constant metal ion concentration (Zn + Ti) of 0.5 mol L⁻¹. This solution is supplied at 5 mL min⁻¹ through the FSP nozzle and dispersed by 5 L min⁻¹ oxygen (pressure drop 1.5 bar) into a fine spray, that is ignited by a ring-shaped flamelet of premixed methane/oxygen (1.25/3.2 L min⁻¹). The so-produced nanoparticles are collected on a glass-fiber filter (GF6 Albet-Hahnemuehle, 257 mm diameter) at 50 cm height above the burner (HAB) by a vacuum pump (Seco SV 1025 C, Busch, Switzerland).

For the sensing films, product nanoparticles are directly deposited²² for 2 min onto 15 mm × 13 mm × 0.8 mm Al₂O₃ substrates (Electronic Design Center, Case Western Reserve University, USA) mounted on a water-cooled holder at a HAB of 20 cm. These substrates feature a set of interdigitated Pt electrodes (sputtered, 350 μ m width and spacing) and a Pt resistance temperature detector (RTD) on the front side. A Pt heater for temperature control is placed on the substrate's back side. In-situ annealing with a particle-free flame improves the adhesion and cohesion of the FSP-deposited particle film.²³ For this, the particle-laden substrate is lowered to a HAB of 14.5 cm and annealed for 30 s by a spray flame (11 mL min⁻¹ xylene dispersed with 5 L min⁻¹ oxygen). Prior to sensing tests, the films are thermally stabilized by 5 h annealing in air at 500 °C inside an oven (Carbolite GmbH).

3.2.2 Particle and film characterization

X-ray diffraction (XRD) is performed with a Bruker AXS D8 Advance diffractometer operated at 40 kV and 30 mA at 2 θ (Cu K_{α}) = 15 - 70°. The scanning step size and speed are 0.0197° and 12° min⁻¹, respectively. Crystal phases are identified with reference structural parameters of wurtzite ZnO

(PDF 79-2205), spinel Zn₂TiO₄ (PDF 86-0155), perovskite ZnTiO₃ (PDF 39-0190), anatase TiO₂ (PDF 21-1272) and rutile TiO₂ (PDF 21-1276). The corresponding crystal sizes are determined with the Rietveld fundamental parameter method, calculated with the software Topas 4.2 (Bruker). Peak shifts and corresponding lattice parameter variations are identified with the software Bruker Diffrac.eva V3.1. To better resolve the peak shifts, a reduced scanning step size (0.0184°) and speed (0.52 ° min⁻¹) are applied. Precise alignment of the patterns is ensured by addition (50 wt%) of crystalline NiO (Sigma Aldrich ~325 mesh, purity 99%) as internal standard.

The specific surface area (SSA) of filter-collected powders is measured by nitrogen adsorption (Micromeritics Tristar 3000). Prior to measurement, samples are degassed for 1 h at 150 °C under nitrogen. The corresponding particle diameters are calculated using densities of wurtzite ZnO (5.67 g cm⁻³), spinel Zn₂TiO₄ (5.32 g cm⁻³), perovskite ZnTiO₃ (5.16 g cm⁻³), anatase TiO₂ (3.79 g cm⁻³) and rutile TiO₂ (4.25 g cm⁻³) based on the nominal particle composition. The density of Ti-doped ZnO solid solutions in the wurtzite crystal configuration is calculated by correcting the wurtzite density with the atomic weight of Ti according to the nominal particle composition, assuming that each Ti substitutes a Zn atom.

Particle images are obtained by transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM), performed on a FEI Talos F200X with high brightness gun (XFEG) operated at 200 kV. The particle samples are prepared by dispersing them with ethanol onto perforated carbon foils supported on copper grids. The STEM images are obtained with a high-angle annular dark field (HAADF) detector providing Z-contrast (i.e. intensity proportional to the atomic number). Energy dispersive X-ray spectroscopy (EDXS) is conducted with four attached

spectrometers (Bruker). The morphology and thickness of the sensing film are analyzed by scanning electron microscopy (SEM) with a Hitachi FE-SEM 4000 operated at 5 kV. For cross-sectional SEM, the sensors are split with a wedge prior to the measurement.

3.2.3 Gas sensing

For electrical characterization, the sensors are mounted on a macor holder and installed in a chamber, described in detail elsewhere.²⁴ The sensors are heated to 250 - 400 °C by powering the substrate's heater with a DC source (R&S HMC8043, Germany). The substrate temperature is monitored continuously by the RTD. The ohmic film resistance between the interdigitated electrodes is measured and recorded with a picoammeter (Keithley, 6487, USA). The sensing measurements are performed at a constant gas flow of 1 L min⁻¹ synthetic air (99.999%, C_nH_m and $NO_x \le 100$ ppb, Pan Gas) resulting in a flow velocity of 0.07 m s⁻¹ over the sensing film. Changing the flow rate down to 0.2 L min⁻¹ should not change the responses, as investigated with a similar type of sensor in an identical chamber.²⁴ The RH (monitored by a Sensirion SHT2x, Switzerland) is set during heat-up at a sensor temperature of 250 °C and a pipe heating of 55 °C (wall temperature) to prevent condensation. The evaluated analyte mixtures are prepared with a mixing set-up described in detail elsewhere.¹⁴ Applied analyte gases are 10 ppm of ethanol, ammonia, acetone and isoprene in N_2 (calibrated mixtures, PanGas). These compounds are selected for their presence in breath and reported interaction (except for isoprene) with ZnO²⁵, making them crucial for a selectivity assessment. The sensor responses to different analytes is calculated as:

$$S = \frac{R_{air}}{R_{analyte}} - 1 \tag{1}$$

where $R_{analyte}$ and R_{air} are the film resistances in air at constant RH with and without a given analyte concentration, respectively. The sensor response time is defined as the time needed to reach 90% of the response resistance change to 20 ppb of isoprene while the recovery time is the one needed to recover 90% of the baseline resistance change. The sensor sensitivity (Σ) is defined as the derivative of the sensor response S with respect to the analyte concentration c, in accordance to the standard DIN 1319-1:1995-01 5.4:

$$\Sigma = \frac{\partial S}{\partial c} \tag{2}$$

3.2.4 In-situ surface characterization during sensing

Reactive surface species and interaction with the analytes at sensor operational conditions are investigated with Diffuse Reflectance Fourier Transform Infrared Spectrometry (DRIFTS, Bruker Vertex 70v with Harrick Sci. Praying Mantis). Therefore, powder samples are dispersed on a flattened internal standard (KBr, Sigma-Aldrich, FT-IR grade, ≥ 99 % trace metal basis) within an in-situ heating cell (Harrick) and compressed slightly. Operating conditions are 325 °C at a total air flow of 50 ml min⁻¹, resulting in a temperature and gas velocity comparable to the sensor test. The RH for DRIFTS is set at 60%. A 500 ppm isoprene in N₂ mixture (calibrated, PanGas) is diluted down to 200 ppm using synthetic air (99.999%, C_nH_m and NO_x \leq 100 ppb, Pan Gas). Prior and during each measurement, samples are stabilized sufficiently long to attain a stable DRIFTS signal. Measurements are performed with a resolution of 4 cm⁻¹ between 4000 and 1100 cm⁻¹ and averaging 40 scans, employing a liquid nitrogen cooled MCT detector (DigiTect, BaF₂ window, 12000 - 850 cm⁻¹ spectral range).

3.3 Results and discussion

3.3.1 Nanostructured Ti-doped ZnO solid solutions from flames

Figure 3.1a shows a schematic of the FSP synthesis of Ti-doped ZnO solid solutions. The metal ions (Ti and Zn) are mixed homogeneously on a molecular level in the organometallic precursor, prior to their spray dispersion and combustion. During particle nucleation, Ti cations are incorporated sufficiently fast²⁶ and form crystalline Ti-doped ZnO solid solution, despite the short residence time at high temperature.²⁷ Moreover, the fast quenching of the product aerosol prevents TiO₂ segregation and preserves the nanostructured dimensions (particle and crystal size)²⁸ of these particles that can be deposited directly onto sensor substrates forming highly porous films.²²

Indeed at 2.5 mol% Ti-doped ZnO, these flame-made particles are ultra-fine and most are smaller than 20 nm (Figure 3.1b). Elemental mapping indicates that Zn (red) and Ti atoms (green) are distributed over the particles (Figure 3.1c,d) suggesting that solid solutions and no segregated ZnO and TiO₂ are formed in the flame. However, Ti seems more present at the particle surface, as supported also by EDX analysis of selected areas (marked by white squares in Figure 3.1d): Ti is detected in an area near the surface (Figure 3.1f) while Ti is not detectable towards the particle-center (Figure 3.1e). Similar observations were made for flame-made Ti-doped SnO₂ solid solutions.²⁹ Note that copper (Cu) and carbon (C) peaks in the EDX spectra are traced to the TEM support grid.

3.3.2 Crystal phase dynamics and Ti incorporation mechanism

Figure 3.2a shows the XRD patterns of as-prepared powders at different Ti content (0 - 100 mol%). Pure ZnO (black pattern) is highly crystalline

and forms the hexagonal wurtzite structure (stars), as indicated by the three characteristic intensity peaks at $2\theta = 31.8$, 34.4 and 36.2° corresponding to the (100), (002) and (101) crystal planes, respectively. This phase is thermodynamically stable³⁰ and has been obtained by FSP before, even at different precursor and flame conditions.²⁸



Figure 3.1: (a) Schematic of the flame spray reactor for production of Ti-doped ZnO solid solution particles and their direct deposition onto sensor substrates. (b) Typical STEM image of 2.5 mol% Ti-doped ZnO indicates the nanostructured morphology (most particles are < 20 nm) of the as-prepared powder. Elemental mapping (smoothed) shows the distribution of (c) Zn (red dots) and (d) Ti (green dots) that are both dispersed over the particles. Note that green dots appear brighter due to neighborhood averaging to make them better visible. Yellow color indicates red overlaid by green. However, Ti seems to be dominantly present at the particle surfaces, as confirmed also by the EDX (e,f) of selected areas in (d).

Most interestingly, adding up to 10 mol% Ti preserves the wurtzite structure and no other crystalline phases (e.g. segregated TiO₂) are formed, similar to wet-made Ti-doped ZnO at comparable dopant levels (~4 mol%).³¹ This is in contrast to the ZnO - TiO₂ phase diagram, where a mixture of ZnO and Zn₂TiO₄ would be expected at equilibrium.³² However,

flame synthesis features fast quenching and that way, even metastable crystal phases can be obtained.³³ Apparently here, Ti is incorporated into the ZnO wurtzite lattice or stays at the surface, as already suggested from EDX analysis (Figure 3.1d-f) and supported by lattice distortions visible in the XRD patterns of Ti-doped ZnO: (a) the (002) peak is lower compared to the (100) and (101) ones than for pure ZnO. This indicates reduced crystal growth in c-direction, possibly hindered by the present Ti-defects as observed for Ti-doped ZnO made by atomic layer deposition¹⁷ and FSP-made Li-doped ZnO while it was even stronger for Sn- and In-doped ZnO.³⁴ (b) The (002) and (101) peaks are shifted toward lower 2θ with increasing Ti content, that is especially visible when magnifying this XRD pattern section (Figure 3.2b). This peak shift indicates an expansion of the lattice cell induced by the Ti-doping, consistent with the literature.¹⁷

The hexagonal close-packed wurtzite structure of pure ZnO consists of alternating planes of Zn and O atoms³⁰ (inset Figure 3.2c, left structure) with lattice dimensions of a = 3.2501 Å and c = 5.2085 Å (Figure 3.2c). When doped with 10 mol% Ti, these increase to 3.2531 and 5.2114 Å, respectively. Interestingly, this expansion is linear with increasing Ti content as typically observed for substitutional incorporation of dopants and described by Vegard's law.³⁵ So Ti seems to substitute Zn at regular cation sites creating point defects as illustrated schematically in the inset of Figure 3.2c (right structure). These Ti cations occur most likely in the Ti⁴⁺ state. In fact, previous X-ray photoelectron spectroscopy³¹ has evidenced the presence of Ti⁴⁺ in wet-made Ti-doped (wurtzite) ZnO solid solutions, while no other multivalent states (i.e. Ti²⁺ or Ti³⁺) were detected. Substitutionally incorporated Ti⁴⁺ could result in the observed expansion of the wurtzite lattice, despite the smaller effective ionic radii of Ti⁴⁺ (42 pm) compared to Zn²⁺ (60 pm) at coordination number IV.³² Actually, lattice expansion can



originate also from additional repulsive force due to the different valency of Zn (2+) and Ti (4+) and locally disturbed coordination.³²

Figure 3.2: XRD patterns of as-prepared powders as a function of Ti content: (a) these consist of ZnO wurtzite (stars), Zn_2TiO_4 spinel, $ZnTiO_3$ perovskite (both diamonds), TiO_2 anatase (circles) and TiO_2 rutile (squares). Adding Ti up to 10 mol% does not alter the ZnO wurtzite configuration but the (002) peaks are reduced and slightly shifted towards smaller 2θ (b), as observed also for the (101) peak. This shift indicates a lattice parameter expansion in a- and c-axis (c) that is linear and could indicate a substitutional incorporation of Ti^{4+} cations, as illustrated on wurtzite unit cells.
When adding 20 and 50 mol% Ti, intermediate spinel Zn_2TiO_4 and/or perovskite ZnTiO₃ (both diamonds in Figure 3.2a) are formed that are present also at phase equilibrium.³⁶ Note, that these phases possess rather similar XRD peak characteristics making them hardly distinguishable. At 100 mol% Ti, crystalline TiO₂ is formed predominantly in the anatase (~85 wt%) and less in the rutile phase, as typically observed for FSP at comparable conditions.³⁷ It should be noted that the subsequent thermal stabilization of the sensing particles by annealing at 500 °C for 5 h before sensor testing did not affect the crystal composition and lattice parameter variations (results not shown here).

3.3.3 Ti-doping effect on particle/crystal size, morphology and thermal stability

The average particle (d_{BET} , triangles) and crystal size (d_{XRD} , squares) as a function of Ti content for the as-prepared powders (filled symbols) are shown in Figure 3.3. Pure ZnO consists of monocrystalline particles with comparable particle and crystal sizes of 19 and 16 nm, respectively, and consistent with literature.²⁸ The particle shape ranges from rather spherical to rod-like (Figure 3.3a) by growing along the c-axis³⁸ of the wurtzite lattice.

When doped with Ti, the crystal and particle sizes decrease with increasing dopant content as incorporated Ti⁴⁺ point defects impede growth during flame synthesis. Also wet-made Ti-doped³⁹ and flame-made Si-doped ZnO showed a similar trend, for the latter possibly due to incorporated Si⁴⁺ but also segregated SiO₂ which is different than here.²⁶ It is interesting to note that Ti-doping also affects particle morphology: at 2.5 mol% Ti, faceted particles (Figure 3.3b) and no rod-like ones as with pure ZnO (Figure 3.3a) are observed. Incorporated Ti⁴⁺ hinders specifically the crystal

growth in c-axis as supported also by the reduced (002) XRD peak compared to pure ZnO (Figure 3.2a). Suppression of ZnO rod formation had been observed also when doped with Fe.⁴⁰



Figure 3.3: Average crystal (d_{XRD} , squares) and particle sizes (d_{BET} , triangles) at different Ti contents for as-prepared (filled symbols) and annealed powders (open symbols) at 500 °C for 5 h. As-prepared pure ZnO forms nanostructured and monocrystalline particles with spherical to elongated (rod-like) morphology, as indicated by TEM (a). During annealing, these particles grow significantly and become all nearly spherical (b). Ti-doping reduces crystal & particle sizes for asprepared powder and almost completely suppresses particle growth during annealing, as confirmed also by TEM for 2.5 mol% Ti (b and d). No formation of rod-like particles is observed for Ti-doped ZnO. Error bars for pure, 2.5 and 10 mol% Ti-doped ZnO indicate the crystal and particle size reproducibility of three identically prepared samples. Some of these bars are smaller than the data symbols.

Notable also, when doping 10 mol% Ti, the average crystal size (7 nm) becomes significantly smaller than the particle size (11 nm), similar to Sidoped ZnO.⁴¹ This is even more pronounced at 50 mol% Ti indicating polycrystallinity. Finally, pure TiO₂ is monocrystalline again with asprepared particle and (anatase) crystal size of 15 nm in good agreement to other FSP-made TiO₂ at similar conditions.³⁷ Such particles are quite reproducible. In fact, the crystal and particle sizes of three identically made samples of pure, 2.5 and 10 mol% Ti-doped ZnO deviate \leq 10% (error bars in Figure 3.3).

During annealing for 5 h at 500 °C (open symbols, Figure 3.3), pure ZnO sinters significantly and more than doubles the particle and crystal size, while reshaping the rod-like particles (Figure 3.3a) to larger spherical-likes (Figure 3.3c). Similar strong crystal growth (from 10.7 to 25.6 nm) had been reported for other flame-made ZnO nanoparticles when annealed for 2 h at 600 °C.²⁶ Most notably, only 2.5 mol% Ti almost completely suppresses this particle and crystal growth, as confirmed also by TEM (Figure 3.3b,d). This highlights the excellent thermal stability of Ti-doped ZnO induced by the incorporated Ti and a similar stabilizing effect had been observed for flame-made Si-doped ZnO²⁶ and MoO₃¹⁴. High thermal stability is a crucial feature for sensing materials to avoid structural aging and thus enable long-term stability of sensors as operational temperatures can be up to 500 °C.³⁷

Such nanoparticles form a highly porous film when deposited directly from the flame onto back-cooled sensor substrates by thermophoresis.²² In fact, SEM (top view) confirms the nanostructured morphology of a 2.5 mol% Ti-doped ZnO film after annealing for 5 h at 500 °C (Figure 3.4a). That fine network consists of aggregated primary particles (inset) with comparable shape and size to the filter-collected ones (Figure 3.3), similar to flame-made (and ammonia-selective) Si-doped MoO₃¹⁴ and SnO₂ films²².

The thickness of such rather uniform films is ca. 5 μ m, as determined from a cross-sectional SEM image (Figure 3.4b). Optimizing the film thickness bears the potential to improve the sensing performance. This can be accomplished easily by varying the FSP deposition time.²² That way, higher responses and faster response and recovery times had been obtained for similar chemoresistive SnO₂.⁴²



Figure 3.4: SEM (a) top view and (b) cross-sectional view of a 2.5 mol% Tidoped ZnO film after annealing at 500 °C for 5 h. Deposited nanoparticles aggregate (inset) and form a fine and highly porous morphology. Such films are rather uniform with a thickness of ca. 5 μ m.

3.3.4 Selective isoprene detection by Ti-doped ZnO

Pure ZnO, TiO₂ and Ti-doped ZnO solid solutions are tested as sensors. Figure 3.5a shows the responses as a function of Ti-content to 500 ppb of isoprene (squares), acetone (circles), ethanol (triangles) and ammonia (diamonds) at 325 °C and breath- realistic 90% RH. Pure ZnO can detect all of these analytes and it shows the strongest response to acetone (0.55), consistent to other pure ZnO sensors operated at 425 °C and dry conditions.²⁵ Doping with Ti turns the ZnO sensors *isoprene-selective*. In fact, increasing the Ti content to 2.5 mol% enhances the isoprene response more than *15 times* from 0.27 to 4.4, while the responses for other analytes increase only slightly (e.g. acetone nearly doubles).

Adding small amounts (< 2.5 mol%) of Ti reduces the particle and crystal size of ZnO (Figure 3.3) by substitutional incorporation of Ti⁴⁺ into the wurtzite lattice (Figure 3.2). That way, sensor responses are increased⁴³ for all analytes (Figure 3.5a). The drastic increase in isoprene response, however, might be associated predominantly to the *surface Ti*⁴⁺ cations (Figure 3.1d). Similar to surface defects of pure ZnO,⁴⁴ such Ti⁴⁺ sites can dissociate water (present in excess at 90% RH) and chemisorb the resulting hydroxyl (OH) groups⁴⁵ that interact with isoprene⁴⁶ and other analytes (e.g. ethanol⁴⁷). Interestingly, surface Ti⁴⁺ seems to promote almost *exclusively* the interaction with isoprene, as indicated by the superior isoprene response and selectivity of Ti-doped ZnO, especially at 2.5 mol% (Figure 3.5a). Regarding sensor reproducibility (error bars), the response variability of three identical sensors (at 1.5, 2.5 and 3.75 mol% Ti-doping) to 500 ppb of isoprene is below $\pm 10\%$.

Above 2.5 and up to 100 mol% Ti content (pure TiO_2), the responses to all analytes deteriorate progressively. This is related probably to reduced charge carrier density with increasing Ti dopant level, as indicated by the

increasing sensor resistance (Figure 3.5a, inset). The ZnO is an n-type semiconductor with electrons as majority charge carrier.⁴⁸ By substituting Zn^{2+} with Ti⁴⁺, a local positive charge excess is generated that is compensated by immobilizing conduction band electrons⁴⁹ in the vicinity of the Ti⁴⁺ sites. Such trapped electrons are not available anymore for chemisorbed OH groups and thus do not contribute to resistance modulation during analyte exposure. This results in reduced responses that, apparently, become significant above 2.5 mol% Ti-content. Despite that, the isoprene selectivity remains high *even* for pure TiO₂ being another indicator that Ti⁴⁺ and related surface species interact *specifically* with isoprene and not with the other analytes. Interestingly, other flame-made but drop-coated TiO₂ showed similar responses to isoprene and acetone at 500 °C in dry air.³⁷

The sensor operating temperature is optimized in the range of 250 to 400 °C for the optimal composition at 2.5 mol% Ti (Figure 3.5b). For isoprene, a volcano-shaped response profile is observed, that is typical for such chemoresistive metal-oxide gas sensors and in agreement to theory⁵⁰. Most notably, a response maximum is located at 325 °C. In contrast, the response to most interfering acetone increases steadily with elevated temperatures, similar to ZnO disks.²⁵ The corresponding isoprene selectivity with respect to the strongest interferent at each temperature peaks also at 325 °C, so this temperature was selected for further testing.

The concentration of isoprene and other markers (e.g. acetone, ammonia and ethanol) can vary significantly in breath. In some cases, the isoprene selectivity of Ti-doped ZnO may be insufficient and this can be overcome by combining the present sensor with other analyte-selective sensors (e.g. Si-doped MoO₃ for ammonia)¹⁴ to an array (E-nose). Such E-noses can trace well individual compounds in gas mixtures, as for example with formaldehyde in mixtures with NH₃, ethanol and acetone at 90% RH.¹⁵



Figure 3.5: (a) Ti-doped ZnO sensor response as a function of Ti content to 500 ppb of isoprene (squares), acetone (circles), ethanol (triangles) and ammonia (diamonds) at 325 °C and 90% RH. Ti-doping turns ZnO isoprene-selective with an optimum response and selectivity at 2.5 mol% Ti. Error bars at this optimum composition indicate the variability of three identically fabricated sensors that is below $\pm 10\%$. The baseline resistance increases with increasing Ti content (inset). (b) Response as a function of the operational temperature for optimally 2.5 mol% Ti-doped ZnO. Optimal isoprene response and selectivity are obtained at 325 °C.

3.3.5 Isoprene interaction with surface species during sensing

In situ DRIFTS is performed to reveal the isoprene interaction of chemisorbed species (e.g. OH) on the sensor surface at operational conditions. Figure 3.6 shows the infrared absorbance spectra of pure ZnO (top), 2.5 mol% Ti-doped ZnO (middle) and pure TiO₂ (bottom) before (solid lines) and after (dashed lines) exposure to 200 ppm of isoprene for 30 min at 325 °C. Note that higher isoprene concentration is used than for sensor testing (Figure 3.5) to make the relevant changes visible, but this should not change the sensing mechanism, similar to CO sensing with SnO₂ at different concentrations.⁵¹ The humidity level is lowered from 90% to 60%, limited by the DRIFTS set-up.



Figure 3.6: IR-absorbance spectra of pure ZnO, 2.5 mol% Ti-doped ZnO and TiO_2 before (solid line) and after (dashed line) exposure to 200 ppm of isoprene for 30 min at 325 °C and 60% RH. Isoprene reduces chemisorbed OH species (3800 - 3000 cm⁻¹) and forms carbonates (1560 and 1440 cm⁻¹). This effect is enhanced at 2.5 mol% Ti-doped ZnO: Ti⁴⁺ surface defects provide additional chemisorption sites (3670 cm⁻¹), compared to ZnO. Isoprene (gray bars) does not chemisorb on the sensor surface.

Before isoprene exposure, pure ZnO contains OH species on its surface as indicated by the broad hump ranging from 3800 to 3000 cm⁻¹ in Figure 3.6, and in particular by the specific peaks assigned to isolated OH (3670 cm⁻¹),⁵² OH bound to O-terminated ZnO (3610 cm⁻¹) and to structural ZnO defects (3550 and 3460 cm⁻¹).⁴⁴ Additional carbonate species are detected from their stretching vibrations⁵³ at 1560 and 1440 cm⁻¹. After exposure to isoprene, less OH groups are present at the surface of pure ZnO confirming that isoprene indeed interacts with OH, consistent with literature.⁴⁶ Interesting also, the carbonate concentration increases possibly being a product of the isoprene reaction with OH. Note that isoprene does not adsorb directly on the surface as indicated by the absence of corresponding absorbance peaks (gray bars at bottom)⁵⁴.

Already at 2.5 mol%, the Ti doping significantly affects the surface chemistry of ZnO by additional formation of Ti⁴⁺-OH, as evidenced⁴⁵ from the increasing peak at 3670 cm⁻¹. Remarkably, this feature is rather distinct despite the low dopant level and probably due to the dominant presence of Ti at the sensor's surface, as suggested already from elemental mapping of such particles (Figure 3.1d). After isoprene exposure, more OH species are removed compared to pure ZnO: while ZnO-related OH species are reduced similarly to pure ZnO, additionally available Ti⁴⁺-OH species intensify the interaction with isoprene in agreement with the observed stronger sensor response (Figure 3.5a). Actually, enhanced isoprene conversion is supported also by the significantly higher formation of carbonate species (1560 and 1440 cm⁻¹) compared to pure ZnO. Note that these isoprene interactions with chemisorbed species are reversible. Finally for pure TiO₂, only Ti⁴⁺-bonded OH groups interact with isoprene and the corresponding change in concentration is weaker than for pure ZnO and 2.5 mol% Ti-doped ZnO, in line with the smaller electrical responses seen above (Figure 3.5a).

3.3.6 Lower detection limit and sensitivity at optimal sensor composition

The optimal sensor composition of 2.5 mol% Ti-doped ZnO is applied to detect even ultra-low, but still relevant isoprene levels below 20 ppb. Such low concentrations can occur particularly in breath of children⁵⁵ and voung adults.⁵⁶ Figure 3.7a shows the resistance change of the sensor (325 °C) when exposed to 20, 10 and 5 ppb of isoprene at breath-realistic 90% RH. When introducing 20 ppb, the film resistance decreases from 37.3 to 27.5 M Ω . This change results in a response of 0.36 that is obtained within a response time of ~1 min, sufficiently fast for online breath evaluation. When flushed with air, the resistance is recovered completely within ~5 min. This indicates fully reversible isoprene interaction without deactivating the Tidoped ZnO sensing structure and it is the same also for the other analytes (ammonia, ethanol and acetone), in agreement to pure ZnO^{25} and TiO_2^{37} sensors at elevated temperature. Most remarkably, isoprene concentrations down to 5 ppb are detected with sufficient (> 10) signal-to-noise ratio and this level is distinguished clearly from 10 and 20 ppb. When repeating the sensor exposure to 10 and 20 ppb, same responses are obtained indicating good reproducibility (Figure 3.7a).

Figure 3.7b shows the sensor calibration for isoprene (0 - 500 ppb) that is nearly linear ($\mathbb{R}^2 > 0.998$) above 20 ppb. Such linear calibrations have been observed also for other metal-oxide sensors (e.g. ZnO with up to 10 ppm ethanol)⁵⁷ and it is consistent with the linear diffusion-reaction theory.⁵⁸ The sensor should also work at higher concentrations, however there, sensor calibration curves are typically non-linear, as demonstrated for ZnO with ethanol⁵⁷. The corresponding sensitivity (Σ) is 9.3 ppm⁻¹ (linear fit) and superior to other pure TiO₂ isoprene detectors ($\Sigma = 1.4$ ppm⁻¹) measured at 500 °C in dry air.³⁷ The detection of breath-relevant isoprene at 90% RH with fast response and recovery times is an important milestone towards a portable isoprene detector for breath analysis. The sensor's robustness to relevant RH fluctuations $(89 - 97\% \text{ RH})^{12}$ should be similar to chemoresistive Si-doped WO₃, that showed only minor response changes (~4.5%) between 80 and 90% RH.²⁴



Figure 3.7: (a) 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. These ultra-low levels are detected with SNR > 10 and clearly distinguished from each other. (b) The sensor calibration curve to isoprene is nearly linear with a sensitivity of 9.3 ppm⁻¹ in the breath-relevant range of 20 to 500 ppb. Such a sensor is rather compact with comparable size to a 1 (ϵ) cent coin (inset).

3.4 Conclusions

Flame-made Ti-doped ZnO *solid solutions* were made in flames and directly deposited onto sensor substrates in a *single step*. Observed lattice distortions (e.g. XRD peak shift) suggest the substitutional incorporation of Ti ($\leq 10 \text{ mol}\%$) into the wurtzite ZnO lattice. Elemental mapping indicates the dominant presence of Ti at the particle surface, in both cases most likely in the Ti⁴⁺ state. This led to superior thermal stability of Ti-doped ZnO, a crucial feature for stable sensor operation.

Adding 1.5 - 2.5 mol% Ti increased the sensor response and selectivity to isoprene and this might be related especially to the Ti⁴⁺ surface sites. These provide additional chemisorbed OH species intensifying the interaction with isoprene during sensing, as observed by *in situ* DRIFTS. Interestingly, above 2.5 mol% Ti, the isoprene responses decreased while preserving the selectivity and this was associated to an apparent reduction of the charge carrier density by the incorporated dopant's trapping of free electrons.

So an optimal combination for isoprene responsiveness and selectivity was identified at 2.5 mol% Ti doping. In fact, this sensor features *superior selectivity* against other typical breath compounds (acetone, ethanol and NH₃) at realistic 90% RH. So it can detect even low breath-relevant isoprene concentrations *down to 5 ppb* sufficiently fast (~1 min) for *real-time* breath analysis. As a result, this sensor is promising as *portable* breath isoprene detector for *non-invasive* monitoring of cholesterol therapy or other chronic diseases and even physical activity.

3.5 References

[1] WHO, Global Health Observatory (GHO) data 2015.

- [2] R. Salerno-Kennedy and K. Cashman, Potential applications of breath isoprene as a biomarker in modern medicine: a concise overview, *Wien. Klin. Wochenschr.*, 2005, 117, 180-186.
- [3] B. G. Stone, T. J. Besse, W. C. Duane, C. Dean Evans and E. G. DeMaster, Effect of regulating cholesterol biosynthesis on breath isoprene excretion in men, *Lipids*, 1993, 28, 705-708.
- [4] T. Karl, P. Prazeller, D. Mayr, A. Jordan, J. Rieder, R. Fall and W. Lindinger, Human breath isoprene and its relation to blood cholesterol levels: new measurements and modeling, *J. Appl. Physiol.*, 2001, 91, 762-770.
- [5] P. Španěl, S. Davies and D. Smith, Quantification of breath isoprene using the selected ion flow tube mass spectrometric analytical method, *Rapid Commun. Mass Spectrom.*, **1999**, 13, 1733-1738.
- [6] S. Davies, P. Španel and D. Smith, A new 'online' method to measure increased exhaled isoprene in end-stage renal failure, *Nephrol. Dial. Transplant.*, 2001, 16, 836-839.
- [7] A. Bajtarevic, C. Ager, M. Pienz, M. Klieber, K. Schwarz, M. Ligor, T. Ligor, W. Filipiak, H. Denz, M. Fiegl, W. Hilbe, W. Weiss, P. Lukas, H. Jamnig, M. Hackl, A. Haidenberger, B. Buszewski, W. Miekisch, J. Schubert and A. Amann, Noninvasive detection of lung cancer by analysis of exhaled breath, *BMC Cancer*, 2009, 9, 1-16.
- [8] N. Alkhouri, T. Singh, E. Alsabbagh, J. Guirguis, T. Chami, I. Hanouneh, D. Grove, R. Lopez and R. Dweik, Isoprene in the Exhaled Breath is a Novel Biomarker for Advanced Fibrosis in Patients with Chronic Liver Disease: A Pilot Study, *Clin. Trans. Gastroenterol.*, 2015, 6, e112.
- [9] A. P. F. Turner and N. Magan, Electronic noses and disease diagnostics, *Nat. Rev. Microbiol.*, **2004**, 2, 161-166.

- [10] C. Hagleitner, A. Hierlemann, D. Lange, A. Kummer, N. Kerness, O. Brand and H. Baltes, Smart single-chip gas sensor microsystem, *Nature*, 2001, 414, 293-296.
- [11] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, J. Breath Res., 2015, 9, 047101.
- [12] L. Ferrus, H. Guenard, G. Vardon and P. Varene, Respiratory water loss, *Respir. Physiol.*, **1980**, 39, 367-381.
- [13] L. Wang, A. Teleki, S. E. Pratsinis and P. I. Gouma, Ferroelectric WO₃ Nanoparticles for Acetone Selective Detection, *Chem. Mater.*, 2008, 20, 4794-4796.
- [14] A. T. Güntner, M. Righettoni and S. E. Pratsinis, Selective sensing of NH₃ by Si-doped α-MoO₃ for breath analysis, *Sens. Actuators B*, 2016, 223, 266-273.
- [15] A. T. Güntner, V. Koren, K. Chikkadi, M. Righettoni and S. E. Pratsinis, E-Nose Sensing of Low-ppb Formaldehyde in Gas Mixtures at High Relative Humidity for Breath Screening of Lung Cancer?, ACS Sens., 2016, 1, 528-535.
- [16] M. Righettoni, A. Schmid, A. Amann and S. E. Pratsinis, Correlations between blood glucose and breath components from portable gas sensors and PTR-TOF-MS, *J. Breath Res.*, 2013, 7, 037110.
- [17] Z.-Y. Ye, H.-L. Lu, Y. Geng, Y.-Z. Gu, Z.-Y. Xie, Y. Zhang, Q.-Q. Sun, S.-J. Ding and D. W. Zhang, Structural, electrical, and optical properties of Ti-doped ZnO films fabricated by atomic layer deposition, *Nanoscale Res. Lett.*, **2013**, 8, 1-6.
- [18] T. Dietl, H. Ohno, F. Matsukura, J. Cibert and D. Ferrand, Zener Model Description of Ferromagnetism in Zinc-Blende Magnetic Semiconductors, *Science*, 2000, 287, 1019-1022.
- [19] J. R. Neal, A. J. Behan, R. M. Ibrahim, H. J. Blythe, M. Ziese, A. M. Fox and G. A. Gehring, Room-Temperature Magneto-Optics of

Ferromagnetic Transition-Metal-Doped ZnO Thin Films, *Phys. Rev. Lett.*, **2006**, 96, 197208.

- [20] P. Sharma, A. Gupta, K. V. Rao, F. J. Owens, R. Sharma, R. Ahuja, J. M. O. Guillen, B. Johansson and G. A. Gehring, Ferromagnetism above room temperature in bulk and transparent thin films of Mn-doped ZnO, *Nat. Mater.*, 2003, 2, 673-677.
- [21] L. Mädler, W. J. Stark and S. E. Pratsinis, Flame-made Ceria Nanoparticles, *J. Mater. Res*, **2002**, 17, 1356-1362.
- [22] L. M\u00e4dler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, *Sens. Actuators B*, **2006**, 114, 283-295.
- [23] A. Tricoli, M. Graf, F. Mayer, S. Kühne, A. Hierlemann and S. E. Pratsinis, Micropatterning Layers by Flame Aerosol Deposition-Annealing, *Adv. Mater.*, 2008, 20, 3005-3010.
- [24] M. Righettoni, A. Tricoli, S. Gass, A. Schmid, A. Amann and S. E. Pratsinis, Breath acetone monitoring by portable Si:WO₃ gas sensors, *Anal. Chim. Acta*, 2012, 738, 69-75.
- [25] M. R. Alenezi, S. J. Henley, N. G. Emerson and S. R. P. Silva, From 1D and 2D ZnO nanostructures to 3D hierarchical structures with enhanced gas sensing properties, *Nanoscale*, 2014, 6, 235-247.
- [26] T. Tani, L. M\u00e4dler and S. E. Pratsinis, Synthesis of zinc oxide/silica composite nanoparticles by flame spray pyrolysis, *J. Mater. Sci.*, 2002, 37, 4627-4632.
- [27] A. J. Gröhn, S. E. Pratsinis, A. Sánchez-Ferrer, R. Mezzenga and K. Wegner, Scale-up of Nanoparticle Synthesis by Flame Spray Pyrolysis: The High-Temperature Particle Residence Time, *Ind. Eng. Chem. Res.*, 2014, 53, 10734-10742.

- [28] T. Tani, L. M\u00e4dler and S. E. Pratsinis, Homogeneous ZnO Nanoparticles by Flame Spray Pyrolysis, J. Nanopart. Res., 2002, 4, 337-343.
- [29] A. Tricoli, M. Righettoni and S. E. Pratsinis, Minimal cross-sensitivity to humidity during ethanol detection by SnO₂-TiO₂ solid solutions, *Nanotechnology*, **2009**, 20, 315502.
- [30] N. N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Butterworth-Heinemann, Oxford, 1984.
- [31] M. Naeem, S. Qaseem, I. H. Gul and A. Maqsood, Study of active surface defects in Ti doped ZnO nanoparticles, J. Appl. Phys., 2010, 107, 124303.
- [32] R. D. Shannon, Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides, *Acta Crystallogr.*, 1976, 32, 751-767.
- [33] R. Strobel and S. E. Pratsinis, Flame aerosol synthesis of smart nanostructured materials, *J. Mater. Chem.*, **2007**, 17, 4743-4756.
- [34] M. J. Height, L. M\u00e4dler, S. E. Pratsinis and F. Krumeich, Nanorods of ZnO Made by Flame Spray Pyrolysis, *Chem. Mater.*, 2006, 18, 572-578.
- [35] L. Vegard, Die Konstitution der Mischkristalle und die Raumfüllung der Atome, Z. Phys. A: Hadrons Nucl., **1921**, 5, 17-26.
- [36] F. H. Dulin and D. E. Rase, Phase Equilibria in the System ZnO— TiO₂, J. Am. Ceram. Soc., 1960, 43, 125-131.
- [37] A. Teleki, S. E. Pratsinis, K. Kalyanasundaram and P. I. Gouma, Sensing of organic vapors by flame-made TiO₂ nanoparticles, *Sens. Actuators B*, 2006, 119, 683-690.
- [38] Z. R. Tian, J. A. Voigt, J. Liu, B. McKenzie, M. J. McDermott, M. A. Rodriguez, H. Konishi and H. Xu, Complex and oriented ZnO nanostructures, *Nat. Mater.*, 2003, 2, 821-826.

- [39] S. Suwanboon, P. Amornpitoksuk and A. Sukolrat, Dependence of optical properties on doping metal, crystallite size and defect concentration of M-doped ZnO nanopowders (M = Al, Mg, Ti), *Ceram. Int.*, 2011, 37, 1359-1365.
- [40] C. Fletcher, Y. Jiang, C. Sun and R. Amal, Morphological evolution and electronic alteration of ZnO nanomaterials induced by Ni/Fe codoping, *Nanoscale*, 2014, 6, 7312-7318.
- [41] L. Mädler, W. J. Stark and S. E. Pratsinis, Rapid synthesis of stable ZnO quantum dots, *J. Appl. Phys.*, **2002**, 92, 6537-6540.
- [42] A. Tricoli and S. E. Pratsinis, Dispersed nanoelectrode devices, *Nat. Nanotech.*, **2010**, 5, 54-60.
- [43] C. Xu, J. Tamaki, N. Miura and N. Yamazoe, Grain size effects on gas sensitivity of porous SnO₂-based elements, *Sens. Actuators B*, **1991**, 3, 147-155.
- [44] M. Ali and M. Winterer, ZnO Nanocrystals: Surprisingly 'Alive', *Chem. Mater.*, **2010**, 22, 85-91.
- [45] P. M. Kumar, S. Badrinarayanan and M. Sastry, Nanocrystalline TiO₂ studied by optical, FTIR and X-ray photoelectron spectroscopy: correlation to presence of surface states, *Thin Solid Films*, **2000**, 358, 122-130.
- [46] T. N. Obee and R. T. Brown, TiO₂ Photocatalysis for Indoor Air Applications: Effects of Humidity and Trace Contaminant Levels on the Oxidation Rates of Formaldehyde, Toluene, and 1,3-Butadiene, *Environ. Sci. Technol.*, **1995**, 29, 1223-1231.
- [47] J. M. Coronado, S. Kataoka, I. Tejedor-Tejedor and M. A. Anderson, Dynamic phenomena during the photocatalytic oxidation of ethanol and acetone over nanocrystalline TiO₂: simultaneous FTIR analysis of gas and surface species, J. Catal., 2003, 219, 219-230.

- [48] Ü. Özgür, Y. I. Alivov, C. Liu, A. Teke, M. A. Reshchikov, S. Doğan,
 V. Avrutin, S.-J. Cho and H. Morkoç, A comprehensive review of ZnO materials and devices, *J. Appl. Phys.*, 2005, 98, 041301.
- [49] W. Choi, A. Termin and M. R. Hoffmann, The Role of Metal Ion Dopants in Quantum-Sized TiO₂: Correlation between Photoreactivity and Charge Carrier Recombination Dynamics, J. Phys. Chem., 1994, 98, 13669-13679.
- [50] G. Sakai, N. Matsunaga, K. Shimanoe and N. Yamazoe, Theory of gas-diffusion controlled sensitivity for thin film semiconductor gas sensor, *Sens. Actuators B*, 2001, 80, 125-131.
- [51] S. Harbeck, A. Szatvanyi, N. Barsan, U. Weimar and V. Hoffmann, DRIFT studies of thick film un-doped and Pd-doped SnO₂ sensors: temperature changes effect and CO detection mechanism in the presence of water vapour, *Thin Solid Films*, 2003, 436, 76-83.
- [52] H. Noei, H. Qiu, Y. Wang, E. Löffler, C. Wöll and M. Muhler, The identification of hydroxyl groups on ZnO nanoparticles by infrared spectroscopy, *Phys. Chem. Chem. Phys.*, 2008, 10, 7092-7097.
- [53] N. O. Savage, S. A. Akbar and P. K. Dutta, Titanium dioxide based high temperature carbon monoxide selective sensor, *Sens. Actuators* B, 2001, 72, 239-248.
- [54] P. J. Linstrom and W. G. Mallard, *NIST Chemistry webbook; NIST standard reference database No. 69*, Gaithersburg, 2016.
- [55] N. Nelson, V. Lagesson, A. R. Nosratabadi, J. Ludvigsson and C. Tagesson, Exhaled Isoprene and Acetone in Newborn Infants and in Children with Diabetes Mellitus, *Pediatr. Res.*, 1998, 44, 363-367.
- [56] D. Smith, P. Španěl, B. Enderby, W. Lenney, C. Turner and S. J. Davies, Isoprene levels in the exhaled breath of 200 healthy pupils within the age range 7–18 years studied using SIFT-MS, *J. Breath Res.*, 2009, 4, 017101.

- [57] Z. Xu, G. Duan, H. Zhang, Y. Wang, L. Xu and W. Cai, In situ synthesis of porous array films on a filament induced micro-gap electrode pair and their use as resistance-type gas sensors with enhanced performances, *Nanoscale*, **2015**, 7, 14264-14271.
- [58] J. W. Gardner, A diffusion-reaction model of electrical-conduction in tin oxide gas sensors, *Semicond. Sci. Technol.*, **1989**, 4, 345-350.

E-nose sensing of low-ppb formaldehyde in gas mixtures at high relative humidity for breath screening of lung cancer?

Abstract Formaldehyde (FA) is a potential breath marker for lung cancer and a tracer for indoor air quality monitoring. 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 electronic nose (E-nose) for real-time quantification of FA at realistic conditions. This E-nose consists of four nanostructured and highly porous Pt-, Si-, Pd- and Ti-doped SnO₂ sensing films directly deposited onto silicon wafer-based microsubstrates by flame spray pyrolysis (FSP). The constituent sensors offer stable responses (24 h tested) and detection of FA 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 FA in 2-, 3- and 4-analyte mixtures by multivariate linear regression. In simulated breath (FA with higher acetone, NH₃ and ethanol concentrations), FA is detected with an average error ≤ 9 ppb using the present E-nose and overcoming selectivity issues of single sensors. This device could facilitate easy screening of lung cancer patients and monitoring of indoor FA concentrations.

4.1 Introduction

Formaldehyde (FA) has been proposed as one of the markers for lung cancer detection from exhaled human breath.¹ Indeed, elevated median levels of 83 ppb were measured in lung cancer patients compared to 48 ppb for healthy ones,² a trend consistent with earlier results³. Lung cancer diagnosis from breath is attractive being non-invasive, inexpensive and easily accessible.⁴ Especially when done with portable and simple-in-use breath analyzers, easy screening of populations is possible. Also in air quality monitoring, FA detection is interesting since it was identified as carcinogenic.⁵ It is released from various indoor sources, including laminated wood-based products or combusted biomass.⁶ Indoor FA levels should not exceed⁷ 100 ppb as long-term exposure to elevated levels increase mortality from nasopharyngeal⁸ and myeloid leukemia.⁹

Both, medical and air quality applications pose a similar challenge to FA analyzers, that is selective sensing typically below 100 ppb at significantly higher interferent gas levels (e.g. in breath 400 - 1'800 ppb NH_3 ¹⁰, including high relative humidity (RH). Inexpensive, portable and simple-in-use chemoresistive FA sensors based on semiconductive metaloxides (MOx) are quite attractive. They offer fast response and recovery times¹¹ suitable for on-line measurement, simple operation and a compact design¹² already applied in portable breath samplers¹³. Additionally, MOx sufficiently low FA levels, especially when sensors can detect nanostructured.¹⁴ Detection of relevant FA levels has been achieved by several MOx including nanostructured doped SnO2¹⁵, nanocrystalline In₄Sn₃O₁₂¹⁶, CuO nanocubes¹⁷ and In₂O₃ nanolamellas¹⁸. However, sufficient FA selectivity in multi-component gas mixtures has not been demonstrated and might not be even possible with single sensors without using new materials such as ε -WO₃ for breath acetone¹⁹ or α -MoO₃ for breath NH₃¹¹.

To overcome this challenge, a viable option is to combine broadly sensitive but differently selective sensors in arrays, so-called electronic noses (E-nose), that mimic the mammalian olfactory system.²⁰ Statistical response analysis is applied to *selectively* detect the concentration of target analytes in mixtures.²¹ That way, 60 ppb of FA were detected in 2-analyte mixtures with different interferent gases (e.g. acetone or ethanol) by an E-nose.¹⁵ It comprised eight SnO₂-based sensors, always two with same dopant (Au, Cu, Pt or Pd) but at different temperature.¹⁵

Flame spray pyrolysis (FSP) is a scalable technique capable of high production rates²² with potential for mass production of MOx sensors by direct deposition of multiple sensors onto silicon substrates.²³ That way, 69 SnO₂-based sensing films have been deposited onto a 4-inch silicon wafer in a single step.²⁴ It is a promising tool to fabricate sensor arrays as a variety of material compositions is accessible allowing easy alteration of sensing characteristics including selectivity.²⁵ These include not just pristine MOx but also more complex multi-component systems, such as solid solutions, segregated mixed oxides or noble metal dopants dispersed on the MOx surface.²² That way, sensing characteristics might be even tailored torward dominantly *analyte-selective* as shown with Cr:WO₃ (acetone)¹⁹ and Si:MoO₃ (NH₃)¹¹. Furthermore, such nanostructured and highly porous²⁶ sensing films can be directly deposited onto micromachined silicon (Si) wafer-based substrates.²³

Here, we present a compact E-nose for FA quantification in realistic gas mixtures. The E-nose consists of four differently doped SnO_2 microsensors assembled to an array. Pt, Si, Ti and Pd are chosen as dopants to induce different analyte selectivity amongst the sensors. The nanostructured and highly porous sensing films are made by FSP and directly deposited onto Si wafer-level substrates. Optimal operational conditions are identified enabling FA detection down to 3 ppb and operational stability under realistic conditions (90% RH). Finally with this E-nose and multivariate linear regression (MVLR), FA is detected *selectively* in simulated breath with higher interfering analyte levels (acetone, NH_3 and ethanol).

4.2 Experimental and methods

4.2.1 Microsubstrate fabrication

The microsensor substrates are prepared on a Si wafer by UV lithography.²⁷ The substrate (Figure 4.1a) features a circularly shaped sensing area (d = 500 μ m) of interdigitated Pt electrodes (line width and spacing 10 μ m) that is encircled by a double meandered Pt heater (line width 50 μ m) to regulate the operating temperature and ensure its uniformity. Such a heater design is often referred to as horizontal approach.²⁷

For the preparation of these substrates, a 4-inch Si wafer is used with 180 nm of thermally grown wet silicon oxide serving as electrical insulation. For patterning the Pt structures using lift-off, the image-reversal resist AZ 5214E (Microchemicals GmbH) is coated and patterned using standard UV lithography (365 nm).²⁷ Next, a 5 nm thick layer of Ti and 70 nm of Pt are deposited by physical vapor deposition (e-beam Evaporation Plassys II, Playssys-Bestek, France) onto the wafer. Ti enhances the adhesion of the Pt elements to the SiO₂ surface.²⁸ Thereafter, metal lift-off is performed by placing the wafer in N-methyl pyrrolidone at 80 °C for 10 minutes and rinsing it with 2-propanol before drying. Each 4-inch Si wafer contains 720 microsensor substrates. Finally, the Si wafer is diced into packages of 5 x 4 substrates that are used for film deposition.



Figure 4.1: Process schematic: (a) microsensor substrate features a circularshaped sensing area with a set of interdigitated Pt electrodes. This is surrounded by a meandered Pt electrode serving as heater and resistance temperature detector (RTD). (b-c) Flame-made sensing particles are accurately deposited by thermophoresis on such substrate packages (5 x 4 microsensors) using a shadow mask. (d) After package dicing, Pt:, Si:, Pd: and Ti:SnO₂ microsensors are combined as array (E-nose) and wire-bonded on a chip carrier. Suspending the sensors minimizes thermal losses and ensures a uniform temperature distribution.

4.2.2 Sensing film production

Doped SnO₂ nanoparticles are made by FSP, schematically shown in Figure 4.1b and described in detail elsewhere.²⁶ The precursor solution for Pd:SnO₂ consists of tin (II) ethylhexanoate (Alfa Aesar, 96 %) and paladium acetylacetonate (Aldrich, \geq 99%) as dictated by the nominal Pd content (1 mol%). Xylene (Aldrich, \geq 99.7%) is admixed to obtain a total metal (Pd and Sn) concentration of 0.5 M. The precursors for Si:SnO₂ (6 mol%)²⁹, Pt:SnO₂ (0.15 mol%)³⁰, and Ti:SnO₂ (4.6 mol%)³¹ are selected and the chosen dopant levels (in parenthesis) had been optimized with respect to sensor performance as in the cited literature. These precursors are fed at 5 ml min⁻¹ through the FSP nozzle and dispersed to a fine spray with 5 L min⁻¹

oxygen at a pressure drop of 1.5 bar. A premixed ring-shaped methane/oxygen flame ($CH_4 = 1.25 \text{ Lmin}^{-1}$, $O_2 = 3.2 \text{ Lmin}^{-1}$) ignites the spray while additional sheath oxygen is fed at 5 Lmin⁻¹ through an annulus surrounding the pilot CH_4/O_2 flame.²⁶

Product nanoparticles are directly deposited by thermophoresis²⁶ on a water-cooled substrate 20 cm above the FSP nozzle for 4 min (Figure 4.1b). Accurate and reproducible deposition in the designated sensing area (Figure 4.1c) is ensured by a shadow mask (stainless steel 1 mm thin) exposing only the interdigitated electrodes. To improve cohesion and adhesion, sensing films are *in-situ* annealed²³ by lowering the nanoparticle-laden substrates to 14.5 cm above the nozzle for 30 s and applying a flame fed with 11 mL min⁻¹ xylene and dispersed by 5 L min⁻¹ oxygen. Additionally, the sensors are thermally stabilized by subsequent annealing for 10 h at 500 °C in an oven (Carbolite GmbH, Germany) to prevent sintering of the sensing structures during sensor operation that would lead to signal drift. Finally, the sensor packages are diced with a cutting tweezer to separate the single sensors. Deposition accuracy and film morphology are investigated by light microscopy (SEM) using a Gemini Leo 1530 (Zeiss, Germany).

4.2.3 Sensor and E-nose evaluation

Four differently doped microsensors (Pt:, Si:, Pd: and Ti:SnO₂) are assembled to an array (E-nose) by wire-bonding (F&K Delvotec, Germany) them on a 14.22 mm x 11.63 mm x 1.4 mm leadless chip carrier (LCC, E-tec Interconnect, Switzerland) using 30 μ m Al wires (Figure 4.1d). By applying double wire bonds, the sensors are suspended to ensure a uniform temperature distribution and minimize the heat-loss by conduction to the LCC. The E-nose is mounted on a socket that is soldered on a printed circuit board (PCB) and placed in a sensor chamber. The chamber consists of a tube (d = 17 mm) with a rectangular space (18.1 mm x 16.6 mm x 18 mm) in the middle, to accommodate the sensor array. The chamber is made of stainless steel for reduced analyte interference³² and is designed to have minimum dead space and recirculation zones.

The gas mixing set-up applied for microsensor/E-nose evaluation is described in more detail elsewhere¹¹. Synthetic air (Pan Gas 5.0, C_nH_m and $NO_x \le 100$ ppb) is used as carrier gas with 90% RH to simulate real breath conditions³³ and this forms the sensor baseline. The analyte gases, FA (10 ppm in N₂, Pan Gas, 5.0), acetone (50 ppm in N₂, Pan Gas 5.0), NH₃ (50 ppm in N₂, Pan Gas 5.0) and ethanol (50 ppm in N₂, Pan Gas 5.0), are dosed to the carrier gas to obtain the desired concentrations. For simulated breath mixtures, 36 (2-analyte) and 60 (3- and 4-analyte) random combinations of breath-realistic FA (30, 60, 90, 120, 150 or 180 ppb), acetone (250, 400, 600, 800, 1'200 or 1'800 ppb)³⁴, NH₃ (250, 500, 800, 1'200, 1'600 or 2'000 $(50, 100, 150, 200, 400 \text{ or } 600 \text{ ppb})^{34}$ concentrations are tested. The total flow rate of the gas mixture over the sensors is kept at 1 L min⁻¹. Sensing film resistances are measured and recorded with a multichannel multimeter (Keithley 2700, USA). A source meter (Keithley 2400, USA) is used to heat the sensors by providing a constant current to the heaters that are connected in series. By additionally placing variable resistors (Cermet-Potentiometer 50 kOhm linear, Vishay, USA) in parallel to each heater, the temperature is adjusted individually and monitored using the Pt heater also as resistance temperature detector (RTD).

4.2.4 Data analysis

The sensor response (S) is defined³⁵ as the ratio of sensor resistance in dry air R_{air} and when subjected to the analyte gas mixture $R_{analyte}$:

$$S = \frac{R_{air}}{R_{analyte}} - 1 \tag{1}$$

Sensor sensitivity (Σ) is defined according to the technical standard DIN 1319-1:1995-01 5.4 as the derivative of sensor response S with respect to analyte concentration c:

$$\Sigma = \frac{\partial S}{\partial c} \tag{2}$$

The Σ is approximated by linear regression from fairly linear sensor calibration lines. The sensor response time is the time needed to reach 90% of the response resistance when exposed to the analyte. The recovery time is the time required to recover 90% of the baseline resistance.

A multivariate linear regression (MVLR) model³⁶ is applied to obtain analyte concentrations c_x (x specifies the analyte) in gas mixtures from the E-nose responses S_i (i specifies the respective sensor):

$$c_x = \sum_{i=1}^4 a_{i,x} \cdot S_i + b_x$$
 (3)

The coefficients $a_{i,x}$ and b_x are obtained from a calibration performed with randomly chosen measurement points. Note that calibration measurements are excluded from those used for extracting the analyte gas concentrations later on. Calculations are done with MATLAB (version R2015b, MathWorks, Massachusetts, USA) and the code is shown in Appendix B. The estimation error is defined as the difference between estimated analyte concentration $c_{x,p}$ and the actual one $c_{x,a}$:

$$\varepsilon = \left| c_{x,p} - c_{x,a} \right| \tag{4}$$

4.3 Results and discussion



4.3.1 Microsensor characterization

Figure 4.2: (a) Sensor package after deposition of a flame-made and in-situ annealed $Si:SnO_2$ film. SEM confirms (b) the accurate sensing film deposition onto the designated area with interdigitated electrodes and indicates (c) the highly porous film architecture favorable for gas sensing. (d) Such sensors are rather small in comparison, for instance, to the index finger.

Figure 4.2a shows a Si:SnO₂ microsensor package (5 x 4 sensors) after sensing film deposition and mechanical stabilization by rapid flame treatment (*in-situ* annealing). Flame-made sensing particles are deposited (black patterns) within the designated area of the interdigitated electrodes (d = 500 μ m), as confirmed also by SEM (Figure 4.2b). The heater and electrode pads are shielded by the shadow mask and not contaminated by particles. Deviation in film size (Figure 4.2a) might result from the fabrication tolerance of the shadow mask as the openings vary slightly with respect to diameter. During deposition by thermophoresis,²⁶ particles form a highly porous and nanostructured network (Figure 4.2c). The subsequent mechanical stabilization by *in-situ* annealing is important as the sensing films need to withstand further processing (e.g. dicing or wire-bonding). The bulk thickness for a SnO₂ film produced under similar conditions was measured from SEM images to be ~1.5 µm, as reported in another study²³.

The applied FSP method is capable to deposit sensing films also onto entire silicon wafers in a single step.²³ Here, each wafer contains 720 microsensor substrates that could be patterned at once. These microsensors (Figure 4.2d) and the corresponding E-nose (Figure 4.1d) are rather compact, so they can be easily incorporated into an already available portable breath sampler.¹³ They can be attached also to other electronic devices to provide additional functionality.

4.3.2 Operational temperature and single sensor stability

As MOx sensors go through response maxima with increasing temperature,³⁷ the effect of operational temperature on individual sensor response to breath-relevant 60 ppb of FA is investigated in the range of 250 - 400 °C at 90% RH (Figure 4.3a). With increasing temperature, Si: (circles), Pd: (squares), Pt: (triangles) and Ti:SnO₂ (diamonds) show increasing response that depends strongly on the individual dopant: at 400 °C, highest response is observed for Si-doping (1.7) while Ti:SnO₂ exhibits the lowest (0.24). Note that the temperature is not further increased to prevent possible sensing film alteration despite the thermal stabilization (500 °C, 5 h) during fabrication. Nanostructures are inherently prone to

sintering³⁸ and high RH (e.g. 90%) might enhance this²¹ leading to a loss of available surface area for sensing. The resulting performance fading would reduce long-term operability of the system. So 400 °C is selected as operational temperature for further testing.



Figure 4.3: (a) Response as a function of operational temperature of Si: (circles), Pd: (squares), Pt: (triangles) and Ti:SnO₂ (diamonds) sensors to breath-relevant 60 ppb of FA at 1 L min⁻¹ air and 90% RH. (b) The average power consumption of a single microheater increases almost linearly with temperature. Error bars indicate the variability of at least four microheaters. (c) At 400 °C, the sensor responses to 60 ppb of formaldehyde are rather stable during 24 h of continuous operation.

The required heating power of a single microsensor at 250 - 400 °C and standard flow conditions of 1 L_n min⁻¹ and 90% RH is shown in Figure 4.3b. The power for these suspended sensors increases almost linearly with temperature, probably by forced convection dominated heat losses. At 400 °C, a heater power of only 522 mW is required, sufficiently low to operate such sensors in a battery-powered portable system. The power consumption could be decreased further by introducing a closed or even suspended heater design²⁷. That way, the heating power can be reduced down to ~30 mW at 400 °C³⁹.

The sensor response stability at 400 °C during 24 h of continuous operation at 90% RH is shown in Figure 4.3c. When exposed to 60 ppb FA every 1.5 h, all sensors exhibit rather stable response with a variation of $\leq 5\%$ and no degradation is visible. The observed excellent stability during 24 h is promising as had been shown for Pt:SnO₂ (also 0.2 wt%) also up to 20 days at 10% RH³⁰. Long life time without the need for frequent tedious re-calibration are attractive features for such a device.

4.3.3 Low-ppb FA detection

FA levels in exhaled breath can be as low as 5 ppb and comparable concentration differences need to be resolved.³ Figure 4.4a shows the resistance change of exemplary Si:SnO₂ (400 °C) when exposed to ultra-low FA levels of 10, 7, 5, and 3 ppb at breath-realistic 90% RH. When injecting 10 ppb, the film resistance decreases from 114 to 93 k Ω corresponding to a response of 0.23. This response is obtained within 140 s and when flushed with air, the baseline is recovered after 190 s. Both indicate rapid and fully reversible interaction of the analyte with the sensing structure. Most notably, FA levels down to 3 ppb are detected with high signal-to-noise ratio (SNR > 25) and this can be clearly distinguished from 5, 7 and 10 ppb.



These sensor responses are nicely reproducible. In fact, when exposing the sensors again to 5 ppb, same response resistances are obtained.

Figure 4.4: (a) Film resistance of a Si:SnO₂ sensor upon exposure to 10, 7, 5, and 3 ppb of FA. These ultra-low analyte levels are detected with sufficient signal-tonoise ratio (SNR, > 25). (b) Sensor calibration curves and sensitivities for formaldehyde detection (5 - 180 ppb) of Si: (circles), Pd: (squares), Pt: (triangles) and Ti:SnO₂ (diamonds). These curves are nearly linear ($R^2 > 0.995$). Error bars indicate the variability of three sensors that is below ±10%. Most such bars are smaller than the data symbol.

To the best of our knowledge, the detection of 3 ppb of FA at such high SNR seems superior to other MOx sensors for FA¹⁵⁻¹⁸. The extrapolated lower limit of detection (LOD) for Si:SnO₂ is 0.1 ppb at SNR = 1. This promising performance could be attributed to the highly porous film architecture of flame-made SnO₂-based sensing films²⁶ (Figure 4.2c). Analyte molecules can easily penetrate into the film and interact with the large available MOx surface area.⁴⁰ Additionally such fine, narrow sensing structures (primary particles & sinter necks) with dimensions approaching twice the SnO₂'s Debye length ($2\delta = 6.9$ nm at 400 °C) show strongly enhanced sensitivity.¹⁴ The baseline resistance of all sensors is below 1 MΩ and therefore suitable for integration into monolithic devices.⁴¹

Figure 4.4b shows the sensor calibration for FA detection (0 - 180 ppb)of Si: (circles), Pd: (squares), Pt: (triangles) and Ti:SnO₂ (diamonds) at 400 °C and 90% RH. Each data symbol represents the average response and error bar obtained from three individual (or singular) sensors with identical composition. The variability is below $\pm 10\%$ highlighting their good reproducibility. The calibration slope corresponds to the sensor's sensitivity and depends strongly on dopant composition. All sensor responses increase linearly ($R^2 > 0.995$) with increasing FA concentration. That way, relevant FA levels can be clearly distinguished. Linear calibration curves are in agreement with measurements of organic vapors below 60 ppm by SnO₂based sensors (Figaro) and supported by theory (linear diffusion-reaction model).³⁷ Calculated sensitivities in Figure 4.4b vary from $\Sigma = 3.7$ to 27.4 ppm⁻¹ for Ti- and Si-doping, respectively. The demonstrated detection of such low FA levels and high sensitivity under breath-realistic conditions (90% RH) are attractive features of these sensors as breath-relevant concentrations² are resolved accurately.



Figure 4.5: Normalized responses of Pt:, Si:, Pd: and Ti:SnO₂ sensors to breathrelevant 60 ppb FA (blue), 600 ppb acetone (grey), 200 ppb ethanol (red) and 800 ppb NH_3 (green). For each sensing material, responses were normalized to the maximum response to better indicate the different selectivities induced by the individual dopants.

In human breath, some analytes are present at high ppb level (e.g. acetone, ethanol or NH_3)⁴² which is much higher than FA. So providing just low LOD and high sensitivity is not sufficient but high *selectivity* is needed as well to accurately quantify breath FA. Figure 4.5 shows the normalized responses of the above sensors at 400 °C to 60 ppb FA² (blue), 600 ppb acetone³⁴ (grey), 200 ppb ethanol³⁴ (red) and 800 ppb NH_3^{10} (green) at 90% RH. The latter three represent typical breath compounds at their realistic level. Note that these responses were normalized with respect to the maximum response of each sensor to simplify a comparison with respect to

selectivity. At a first glance, all sensors are responsive to every analyte and the individual dopants induce different selectivity. SnO₂ is well-known for its *non-selective* sensing behavior and dopants narrow this down.⁴³ Most sensors respond dominantly to acetone and ethanol and less to FA (except for Pd:SnO₂) and NH₃. None of them shows the required high FA *selectivity* necessary to correctly quantify breath FA with a single sensor. However, this challenge is overcome by combining them in an array (E-nose) where their *differences in selectivity* are exploited by statistical analysis.

4.3.5 E-nose sensing in 2-analyte mixtures

Figure 4.6a shows the sensor calibration curves (dashed lines) of exemplary Pt:SnO₂ (400 °C) for FA (0 - 180 ppb) at different interfering acetone levels (0 - 1'800 ppb) and 90% RH. Interestingly, these calibration curves are still linear ($R^2 > 0.98$) despite the high interfering acetone concentrations. Starting at 0 ppb acetone which is identical to the Pt:SnO₂ (triangles) in Figure 4.4b, all curves are shifted upwards with increasing acetone concentration. This indicates that responses to both analytes are superimposed somehow and not distinguishable from each other as already expected from their lack of sensor selectivity (Figure 4.5). Semiconducting MOx sensors have linear transfer characteristics at the low concentrations (< 60 ppm)³⁷ of both analytes here.

However, the sensitivity to FA of the individual sensors (slope of their calibration curve) could be affected by the presence of acetone (Figure 4.6b). Especially for Si:SnO₂ (circles), it is halved when introducing only 400 ppb of acetone. This could indicate an interaction between acetone and FA but also a competition for available adsorption sizes and/or chemisorbed species on the Si:SnO₂ surface is quite likely, despite the extremely low analyte concentrations.



Figure 4.6: (a) Calibration curves of a Pt:SnO₂ sensor for FA detection (0 - 180 ppb) at higher acetone interferent levels (0 - 1'800 ppb). These curves are nearly linear ($R^2 > 0.98$) despite the interfering acetone. (b) FA sensitivities of Si: (circles), Pd: (squares), Pt: (triangles) and Ti:SnO₂ (diamonds) at different interfering acetone levels. Sensitivities are reduced (depending on dopant composition) when introducing up to 400 ppb of acetone but hardly change above that.

When further increasing the acetone level, the sensitivity to FA does not change further. Interesting also, this reduction is less pronounced for other doped-SnO₂. A similar trend in reduction of the FA sensitivity is
observed in 2-analyte mixtures with ethanol as background, while NH_3 has no significant effect. Despite that, the reason for this sensitivity reduction is not understood yet, so further research needs to be done to clarify this.

Two conclusions can be drawn for sensor and E-nose calibration: (1) even in gas mixtures with highly diluted analytes, sensor calibration and thus sensitivity to an analyte might be interfered by other gases. So calibration of a sensor system for application in gas mixtures should be performed. (2) The degree of sensitivity interference seems to depend also on the sensing material composition and needs to be carefully investigated. It should be noted that acetone in the breath is typically above 250 ppb,³⁴ so in the region where the sensitivity did not change anymore. In consideration of these observations, the application of a MVLR seems a reasonable first approach to map the E-nose sensor responses on the entire analyte matrix. That way, estimation of FA in simulated breath can be accomplished overcoming selectivity issues of single sensors.

First, the E-nose and subsequent response analysis by MVLR are tested on 2-analyte mixtures. FA (30 - 180 ppb) is estimated at varying acetone interference (250 - 1'800 ppb) and 90% RH. Figure 4.7a shows the average FA estimation against the actual level (dashed line) in 21 different mixtures. The error bars indicate the corresponding estimation deviation of same FA levels. Breath-relevant FA is accurately quantified throughout the entire range with low average estimation error (ε_{avg}) of only 4 ppb. Estimation of the interfering acetone level was done as well with $\varepsilon_{avg} = 12$ ppb (Figure 4.7b). Both results confirm the suitability of the MVLR model for response analysis of this E-nose in gas mixtures. Comparable ε_{avg} of 3 ppb was reported when estimating 60 ppb of FA by eight SnO₂-based sensors and multilayer neural network analysis.¹⁵ However there¹⁵, gas mixtures were encompassing only 60 ppb of FA at 600, 750 & 1'000 ppb of acetone and dry conditions.



Figure 4.7: E-nose estimation in 2-analyte mixtures of (a) FA (30 - 180 ppb) and (b) acetone (250 - 1'800 ppb) in simulated breath by multivariate linear regression (MVLR). Both analytes are estimated very accurately with low errors of $\varepsilon_{avg} = 4$ and 12 ppb, respectively. Symbols and error bars indicate estimation average and variability for different interferent gas levels. The insets show average estimation errors as function of the number of calibration points.

The model was calibrated with an optimum of 15 calibration points of randomly selected mixtures that were separated from estimated ones. This optimum was determined by testing different numbers of calibration points and evaluation of the resulting ε_{avg} . As shown in the insets of Figure 4.7,b, the ε_{avg} levels off at 15 and 10 calibration points for FA and acetone, respectively. A residual ε_{avg} cannot be eliminated even at a higher number. The reason for this might be that FA calibration curves are not perfectly linear ($R^2 = 1$) as can be seen in Figure 4.6a. Furthermore, the tested FA range included acetone interferent levels (e.g. 250 ppb) where the sensitivity to FA still changed (Figure 4.6b). Both non-linearities are not captured by the model and possibly contribute to the residual ε_{avg} .

4.3.6 3- and 4-analyte mixtures

To challenge the E-nose sensing and analysis even further, NH₃ and ethanol are added to the simulated breath mixture next to FA, acetone and 90% RH. Figure 4.8 shows estimated FA levels (30 – 180 ppb) against the actual ones (dashed line) in 3- (black squares) and 4-analyte (red circles) mixtures with acetone (250 - 1'800 ppb), NH₃ (250 – 2'000 ppb) and ethanol (50 – 600 ppb), respectively. Again, the entire FA range is clearly resolved with ε_{avg} of 6 and 9 ppb in 3- and 4-analyte mixtures, respectively. So ε_{avg} increases with size of the analyte mixture. Nevertheless, the lung cancer average² of 90 ppb of FA is still estimated well with 96 ± 8 ppb in 4-analyte mixtures and discriminated clearly from the healthy average of 60 ppb² estimated with 63 ± 11 ppb. The 180 ppb FA is slightly under-estimated in both, 3- and 4-analyte mixtures. Note that calibration was done with 15 and 20 mixtures for the 3- and 4-analyte model, respectively. Other gases are estimated with ε_{avg} of 41 ppb (acetone) and 188 ppb (NH₃) for 3-analyte mixtures and 48 ppb (acetone), 235 ppb (NH₃) and 28 ppb (ethanol) for 4-analyte mixtures respectively.



Figure 4.8: E-nose estimation of FA at 90% RH and in breath-relevant (a) 3-(squares) and (b) 4-analyte mixtures (circles) consisting of FA (30 - 180 ppb), acetone (50 - 1'800 ppb), NH₃ (250 - 2'000 ppb) and ethanol (50 - 600 ppb). FA levels are estimated accurately with low error $\varepsilon_{avg} = 6$ and 9 ppb, respectively, despite the significantly higher interferent gas concentrations. Symbols and error bars indicate estimation average and variability for different interferent levels.

This detection of relevant FA levels by the flame-made E-nose in breath-realistic gas mixtures is an important step towards a portable breath FA analyzer. The analysis of more complex gas mixtures (such as breath) with such E-noses is possible and it has been demonstrated before⁴⁴. The present device could have potential use in lung cancer screening of wide populations. Nevertheless, further work needs to be carried out, i.e. (a) assess and cross-validate the E-nose with humans, (b) further specify healthy and disease-related concentration as there is deviation in the literature^{2,3} and, if possible, (c) define thresholds to classify lung cancer and

healthy states, a difficult task considering that healthy and disease-related FA ranges overlap.^{2,3} Lung cancer typically alters not just FA but an entire pattern of exhaled analytes,¹ so detection of additional markers could improve the reliability of the classification.

4.4 Conclusions

An E-nose was developed for detecting formaldehyde at high RH and in the presence of breath-relevant acetone, NH₃ and ethanol. It consisted of differently doped (Pt, Si, Pd and Ti) SnO₂ sensors made rapidly by flexible flame spray pyrolysis (FSP) and directly deposited onto Si-wafer microsubstrates. The resulting patterns are well-defined, highly porous and nanostructured. Such individual sensors detect ultra-low FA levels down to 3 ppb (SNR > 25) at breath-realistic 90% RH, not met by MOx sensors before (to the best of our knowledge) and related probably to the favorable film architecture here. The low response times (140 s) would be sufficiently fast for real-time breath evaluation. Application of different dopants alters the sensor selectivity, however, not enough for *selective* FA detection by single sensors at high interferent gas levels present typically in breath.

This can be overcome by combining four differently-doped sensors to an electronic nose (E-nose) and subsequent statistical response analysis. The presence of background analytes reduced the sensor's sensitivity to FA, despite their extremely dilute concentration. This reduction depends strongly on the dopant and necessitates sensor calibration in gas mixtures.

Finally, quantification of breath-relevant FA levels (0-180 ppb) is demonstrated with the E-nose and multivariate linear regression in simulated breath: 90% RH and realistic highly interfering levels of acetone, ethanol and NH₃. The entire FA range is estimated accurately with average error ≤ 9 ppb in up to 4-analyte mixtures. Furthermore, lung cancer-related average FA levels are distinguished clearly from the corresponding healthy ones. This device can be readily incorporated into a portable breath sampler¹³ with high potential for easy lung cancer screening of a wide-spread population. Promising would be also its application in indoor air quality monitoring of FA that is carcinogenic.

4.5 References

- M. Hakim, Y. Y. Broza, O. Barash, N. Peled, M. Phillips, A. Amann and H. Haick, Volatile Organic Compounds of Lung Cancer and Possible Biochemical Pathways, *Chem. Rev.*, 2012, 112, 5949-5966.
- [2] P. Fuchs, C. Loeseken, J. K. Schubert and W. Miekisch, Breath gas aldehydes as biomarkers of lung cancer, *Int. J. Cancer*, 2010, 126, 2663-2670.
- [3] A. Wehinger, A. Schmid, S. Mechtcheriakov, M. Ledochowski, C. Grabmer, G. A. Gastl and A. Amann, Lung cancer detection by proton transfer reaction mass-spectrometric analysis of human breath gas, *Int. J. Mass spectrom.*, 2007, 265, 49-59.
- [4] M. Phillips, Breath tests in medicine, *Sci. Am.*, **1992**, 267, 74-79.
- [5] International Agency for Research on Cancer, *IARC classifies* formaldehyde as carcinogenic to humans, IARC, Lyon, 2004; Vol. 15.
- [6] T. Salthammer, S. Mentese and R. Marutzky, Formaldehyde in the Indoor Environment, *Chem. Rev.*, **2010**, 110, 2536-2572.
- [7] R. Golden, Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards, *Crit. Rev. Toxicol.*, 2011, 41, 672-721.
- [8] M. Hauptmann, J. H. Lubin, P. A. Stewart, R. B. Hayes and A. Blair, Mortality from Solid Cancers among Workers in Formaldehyde Industries, Am. J. Epidemiol., 2004, 159, 1117-1130.

- [9] M. Hauptmann, P. A. Stewart, J. H. Lubin, L. E. Beane Freeman, R. W. Hornung, R. F. Herrick, R. N. Hoover, J. F. Fraumeni, A. Blair and R. B. Hayes, Mortality From Lymphohematopoietic Malignancies and Brain Cancer Among Embalmers Exposed to Formaldehyde, *J. Natl. Cancer Inst.*, 2009, 101, 1696-1708.
- [10] S. Davies, P. Spanel and D. Smith, Quantitative analysis of ammonia on the breath of patients in end-stage renal failure, *Kidney Int.*, 1997, 52, 223-228.
- [11] A. T. Güntner, M. Righettoni and S. E. Pratsinis, Selective sensing of NH3 by Si-doped α-MoO3 for breath analysis, Sens. Actuators B, 2016, 223, 266-273.
- [12] M. Graf, U. Frey, S. Taschini and A. Hierlemann, Micro Hot Plate-Based Sensor Array System for the Detection of Environmentally Relevant Gases, *Anal. Chem.*, 2006, 78, 6801-6808.
- [13] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, J. Breath Res., 2015, 9, 047101.
- [14] H. Ogawa, M. Nishikawa and A. Abe, Hall measurement studies and an electrical conduction model of tin oxide ultrafine particle films, J. Appl. Phys., 1982, 53, 4448-4455.
- [15] P. Lv, Z. Tang, G. Wei, J. Yu and Z. Huang, Recognizing indoor formaldehyde in binary gas mixtures with a micro gas sensor array and a neural network, *Meas. Sci. Technol.*, 2007, 18, 2997-3004.
- [16] J. A. Kemmler, S. Pokhrel, J. Birkenstock, M. Schowalter, A. Rosenauer, N. Bârsan, U. Weimar and L. Mädler, Quenched, nanocrystalline $In_4Sn_3O_{12}$ high temperature phase for gas sensing applications, *Sens. Actuators B*, **2012**, 161, 740-747.
- [17] H. J. Park, N. J. Choi, H. Kang, M. Y. Jung, J. W. Park, K. H. Park and D. S. Lee, A ppb-level formaldehyde gas sensor based on CuO

nanocubes prepared using a polyol process, Sens. Actuators B, 2014, 203, 282-288.

- [18] F. Fang, L. Bai, H. Sun, Y. Kuang, X. Sun, T. Shi, D. Song, P. Guo, H. Yang, Z. Zhang, Y. Wang, J. Luo and J. Zhu, Hierarchically porous indium oxide nanolamellas with ten-parts-per-billion-level formaldehyde-sensing performance, *Sens. Actuators B*, **2015**, 206, 714-720.
- [19] L. Wang, A. Teleki, S. E. Pratsinis and P. I. Gouma, Ferroelectric WO₃ Nanoparticles for Acetone Selective Detection, *Chem. Mater.*, 2008, 20, 4794-4796.
- [20] K. Persaud and G. Dodd, Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose, *Nature*, 1982, 299, 352-355.
- [21] S. M. Scott, D. James and Z. Ali, Data analysis for electronic nose systems, *Microchim. Acta*, **2006**, 156, 183-207.
- [22] R. Strobel and S. E. Pratsinis, Flame aerosol synthesis of smart nanostructured materials, *J. Mater. Chem.*, **2007**, 17, 4743-4756.
- [23] A. Tricoli, M. Graf, F. Mayer, S. Kühne, A. Hierlemann and S. E. Pratsinis, Micropatterning Layers by Flame Aerosol Deposition-Annealing, *Adv. Mater.*, 2008, 20, 3005-3010.
- [24] S. Kühne, M. Graf, A. Tricoli, F. Mayer, S. E. Pratsinis and A. Hierlemann, Wafer-level flame-spray-pyrolysis deposition of gassensitive layers on microsensors, J. Micromech. Microeng., 2008, 18, 035040.
- [25] T. Sahm, L. M\u00e4dler, A. Gurlo, N. Barsan, S. E. Pratsinis and U. Weimar, Flame spray synthesis of tin dioxide nanoparticles for gas sensing, *Sens. Actuators B*, 2004, 98, 148-153.
- [26] L. Mädler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films

by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, *Sens. Actuators B*, **2006**, 114, 283-295.

- [27] I. Simon, N. Bârsan, M. Bauer and U. Weimar, Micromachined metal oxide gas sensors: opportunities to improve sensor performance, *Sens. Actuators B*, 2001, 73, 1-26.
- [28] W.-Y. Chung, C.-H. Shim, D.-D. Lee and S.-D. Choi, Tin oxide microsensor for LPG monitoring, Sens. Actuators B, 1994, 20, 139-143.
- [29] A. Tricoli, M. Graf and S. E. Pratsinis, Optimal Doping for Enhanced SnO₂ Sensitivity and Thermal Stability, *Adv. Funct. Mater.*, 2008, 18, 1969-1976.
- [30] L. M\u00e4dler, T. Sahm, A. Gurlo, J. D. Grunwaldt, N. Barsan, U. Weimar and S. E. Pratsinis, Sensing low concentrations of CO using flamespray-made Pt/SnO₂ nanoparticles, *J. Nanopart. Res.*, 2006, 8, 783-796.
- [31] A. Tricoli, M. Righettoni and S. E. Pratsinis, Minimal cross-sensitivity to humidity during ethanol detection by SnO₂-TiO₂ solid solutions, *Nanotechnology*, 2009, 20, 315502.
- [32] W. Cao and Y. Duan, Current status of methods and techniques for breath analysis, *Crit. Rev. Anal. Chem.*, **2007**, 37, 3-13.
- [33] L. Ferrus, H. Guenard, G. Vardon and P. Varene, Respiratory water loss, *Respir. Physiol.*, **1980**, 39, 367-381.
- [34] A. M. Diskin, P. Spaněl and D. Smith, Time variation of ammonia, acetone, isoprene and ethanol in breath: a quantitative SIFT-MS study over 30 days, *Physiol. Meas.*, 2003, 24, 107.
- [35] M. Righettoni, A. Tricoli and S. E. Pratsinis, Si:WO₃ Sensors for Highly Selective Detection of Acetone for Easy Diagnosis of Diabetes by Breath Analysis, *Anal. Chem.*, **2010**, 82, 3581-3587.

- [36] K. V. Mardia, J. T. Kent and J. M. Bibby, *Multivariate analysis*, Academic press, London, 1979.
- [37] J. W. Gardner, A diffusion-reaction model of electrical-conduction in tin oxide gas sensors, *Semicond. Sci. Technol.*, **1989**, 4, 345-350.
- [38] B. Buesser, A. J. Gröhn and S. E. Pratsinis, Sintering Rate and Mechanism of TiO2 Nanoparticles by Molecular Dynamics, J. Phys. Chem. C, 2011, 115, 11030-11035.
- [39] J. W. Gardner, A. Pike, N. F. de Rooij, M. Koudelka-Hep, P. A. Clerc, A. Hierlemann and W. Göpel, Integrated array sensor for detecting organic solvents, *Sens. Actuators B*, **1995**, 26, 135-139.
- [40] N. Barsan and U. Weimar, Conduction Model of Metal Oxide Gas Sensors, J. Electroceram., 2001, 7, 143-167.
- [41] M. Graf, D. Barrettino, S. Taschini, C. Hagleitner, A. Hierlemann and H. Baltes, Metal Oxide-Based Monolithic Complementary Metal Oxide Semiconductor Gas Sensor Microsystem, *Anal. Chem.*, 2004, 76, 4437-4445.
- [42] T. H. Risby and S. F. Solga, Current status of clinical breath analysis, *Appl. Phys. B*, 2006, 85, 421-426.
- [43] J. F. McAleer, P. T. Moseley, J. O. W. Norris, D. E. Williams, P. Taylor and B. C. Tofield, Tin oxide based gas sensors, *Mater. Chem. Phys.*, **1987**, 17, 577-583.
- [44] A. P. F. Turner and N. Magan, Electronic noses and disease diagnostics, *Nat. Rev. Micro.*, 2004, 2, 161-166.

Zeolite membranes for highly selective breath sensors

Abstract Human breath is rich in physiological information, so tracing exhaled molecules with modern chemical gas sensors (e.g. chemoresistive SnO_2) could represent a new generation of hand-held and non-invasive medical diagnostic devices. While being extremely compact, inexpensive and highly sensitive, their success is still limited by selectivity tough. Here, we combine sensors with highly selective *zeolite membranes* pre-separating gas mixtures. Zeolites - broadly applied in catalysis and gas separation effectively separate molecules based on kinetic diameter, sorption and diffusion characteristics. Therefore, zeolite membranes are suitable filters for gas sensors removing undesired species from mixtures like exhaled breath. As proof-of-concept, a zeolite MFI/Al₂O₃ membrane is placed upstream a highly sensitive but weakly selective Pd-doped SnO₂ sensor. Their combination exhibits exceptional selectivity (>100) for formaldehyde down to 30 ppb at 90% relative humidity, 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 and gas sensor types can be realized in the modular sensing device. This could enable a new class of highly sensitive and selective portable breath detectors or compact indoor air monitors.

5.1 Introduction

Breath analysis is simple-in-use, fast and non-invasive and thus ideal to complement medical diagnostics where conventional methods are too costly and cumbersome to employ.¹ This includes, for instance, the rapid and inexpensive lung cancer screening of widespread populations². Modern chemical gas sensors (e.g. chemoresistive SnO₂³) are particularly suitable for hand-held breath analyzers due to their extremely compact design^{4,5}, simple application⁶ and low cost in contrast to gas chromatography-/mass spectrometry-based techniques. While featuring sufficiently low detection limits, however, their lack of *selectivity* remains a major limitation. Despite extensive research in the last decades, only a few selective chemoresistive sensing materials have been developed (e.g. Ti-doped ZnO for isoprene⁷ or Si-doped MoO₃ for ammonia⁸) while sensor arrays (E-noses)⁹ always involve statistical errors when tracing analytes (e.g. formaldehyde¹⁰). What is truly needed are novel strategies that complement chemoresistive sensing.

Filters allow selectivity adjustment independent of sensor design and composition by pre-separating the gas mixture¹¹ (e.g. breath). Especially promising are zeolites, crystalline aluminosilicates with three-dimensional framework exhibiting well-defined pore sizes in the nano- and subnanometer range.¹² Their separation characteristics are governed by the pore structure as well as the chemical composition and allow to filter gas molecules based on kinetic diameter, sorption and diffusion characteristics.¹² By chemical and structural framework modification the separation properties of zeolites are *widely tunable* and thus can be matched to target analytes. Zeolite particles are broadly applied in catalysis¹³ and gas separation¹⁴⁻¹⁶, typically in the form of packed beds. Zeolite membranes^{14,17}, however, should be very suitable filters for sensors in breath analysis since they effectively remove

molecules larger than the zeolite pore size¹⁸. In contrast, packed beds only capture molecules smaller than the pore size until saturation¹⁹.



Figure 5.1: (a) Concept of the membrane-sensor assembly for selective analyte detection. A microporous membrane pre-separates gas mixtures and ideally allows only a target analyte (green) to permeate through. A chemoresistive sensor placed downstream detects the analyte resulting in an electrical signal correlated to its concentration. (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. (e) Image of the compact sensor that features a sensing film, as shown by top-view SEM (f). (g) This film consists of flame-made Pd-doped (1 mol%) SnO₂ nanoparticles that aggregate to a fine and extremely porous network.

Here, we explore the strategy of combining highly sensitive chemoresistive gas sensors with *microporous membranes*, as illustrated schematically in Figure 5.1a. In principle, the supported membrane with specific molecular sieving and adsorption properties pre-separates the gas mixtures (e.g. breath) while a chemoresistive sensor placed downstream quantifies the target analyte (green). Since sensor and membrane are *decoupled*, they can be fabricated individually and operated independently to achieve optimal sensitivity and selectivity. As a proof-of-concept, a Pd-doped SnO₂ sensor is combined with a zeolite MFI membrane on Al_2O_3 support for selective detection of formaldehyde, a potential lung cancer breath marker²⁰ and carcinogenic²¹ indoor air pollutant. The effect of the membrane on sensor performance is evaluated in breath-relevant gas mixtures and benchmarked against state-of-the-art formaldehyde detectors.

5.2 Experimental

5.2.1 Membrane fabrication

The precursor solution for MFI-type zeolite crystals is prepared as follows:²² 1.44 g sodium hydroxide (97%, Sigma-Aldrich) are dissolved in 100 ml tetra-propyl-ammonium hydroxide (TPA(OH), 1 M in H₂O, Sigma-Aldrich) in a closed Teflon flask. Then, 20 g of fumed silica (Aerosil 200, Evonik) are added after heating to 85 °C and dissolved under vigorous stirring and reflux. Subsequently, 3.2 mL of deionized water are added followed by heating to 105 °C for 15 min. The solution is cooled to room temperature within 45 min and aged for 135 min. The membranes are prepared by placing up to four porous and polished alumina disks with 16.3 mm diameter and 0.5 mm thickness in a 250 mL Teflon beaker. The MFI precursor solution is added, the Teflon beaker sealed in a stainless steel autoclave and heated for 8 h at 185 °C, according to Dong et al.²³. Drying of the membranes is carried out at 50 °C for at least 3 days in an oven. Finally,

the tetra-propyl-ammonium (TPA) structuring template is removed by heating the membranes to 450 °C for 6 h.

5.2.2 Membrane characterization

The micropore size distribution of the zeolite powder is assessed by nitrogen sorption (3-Flex, Micrometrics) in the range of $4.5 \cdot 10^{-7} \le p/p_0 \le$ 0.047. The data are analyzed by the Horwath-Kawazoe method that assumes cylindrical pore shape, consistent with the MFI zeolite shape¹⁴. Prior to analysis, the sample was degassed overnight at 250 °C. The macropore size distribution of the alumina support is determined by nitrogen sorption (TriStar 3000, Micromeritics) in the pressure range of $0.05 \le p/p_0 \le 0.99$ after degassing at 5.10⁻² mbar and 150 °C for 1 h. The data are analyzed according to the Barrett-Joyner-Halenda method. The film morphology of the membrane and sensing film is investigated by scanning electron microscopy (S-4800, Hitachi) operated at 3 kV. The crystalline compositions of the substrate, zeolite powder and membranes are determined by X-ray diffraction (XRD; Bruker AXS D8 Advance) operated at 40 kV and 30 mA at 2 θ (Cu K_{α}) = 5 - 80° and a step size of 0.0145°. Crystal phases are identified from structural parameters of α -Al₂O₃ (ICSD 85137) and zeolite MFI (ICSD 34370). The Rietveld refinement method is applied to determine the corresponding crystal sizes.

5.2.3 Sensor fabrication

Pd-doped SnO₂ nanoparticles are made by flame spray pyrolysis (FSP) and deposited directly²⁴ onto silicon wafer-based microsubstrates¹⁰. The FSP precursor solution of tin (II) ethylhexanoate (Alfa Aesar, 96 %), palladium acetylacetonate (Aldrich, \geq 99%) and xylenes (Aldrich, \geq 99.7%) is adjusted to achieve a total metal (Pd and Sn) concentration of 0.5 M and a product Pd content of 1 mol%. This precursor is supplied at 5 ml min⁻¹ to the FSP

reactor, atomized by 5 L min⁻¹ oxygen (1.5 bar pressure drop) to a fine spray and ignited by a flamelet while providing 5 L min⁻¹ sheath oxygen. Product nanoparticles are deposited directly onto circularly-shaped interdigitated Pt electrodes (d = 500 μ m) on water-cooled microsubstrates and mechanically stabilized by in situ annealing, as described elsewhere¹⁰. Subsequent annealing at 500 °C for 10 h in an oven (Carbolite GmbH, Germany) thermally stabilizes the sensing film.

5.2.4 Gas detector evaluation

Before testing, sensors are wire-bonded on a chip carrier and mounted on a socket (LCC-032-H210-55, E-tec Interconnect) that is installed inside a rectangular cavity (18.1 mm x 16.6 mm x 18 mm) in a stainless steel chamber (please see Appendix Figure C.1). The sensors are operated at 400 °C by providing constant voltage to the substrate-mounted Pt-heaters while using the same as resistance temperature detector (RTD). Sensor film resistances are measured continuously with a multimeter (Keithley 2700). The membrane is placed at the cavity inlet, 7 mm from the sensor to separate the sensor from the gas flow and to minimize membrane heat up by the sensor. Note that experiments are conducted also without membrane for reference. In sensing experiments, 600 ml min⁻¹ of gas are passed over the membrane while the sensor cavity is not flushed and kept at atmospheric pressure. Synthetic air (PanGas 5.0, C_nH_m and $NO_x \le 100$ ppb) is applied as carrier gas and humidified with a water bubbler to achieve the desired relative humidity (RH), as verified with a humidity sensor (SHT21, Sensirion). Analyte gases (all PanGas 5.0) are dosed with a mixing set-up described in detail elsewhere.⁸ These are formaldehyde (10 ppm in N_2), acetone (10 ppm in N₂), ethanol (10 ppm in syn. air), methanol (10 ppm in syn. air), NH₃ (10 ppm in syn. air), isoprene (10 ppm in syn. air). For TIPB (95 %, Sigma-Aldrich), 5 ml of liquid TIPB contained in a 50 ml wide neck flask are slowly evaporated at room temperature into a synthetic air stream. Desired TIPB concentrations are obtained by adjusting the air flow, following calibration with a proton transfer reaction time-of-flight mass spectrometer (PTR-TOF-MS1000, Ionicon).

5.3 Results and Discussion

5.3.1 Membrane and sensor characterization

Figure 5.1b shows the coin-type membrane comprising a compact and coherent ~3 μ m zeolite MFI film (Figure 5.1c, brown-shaded) hydrothermally grown on a porous Al₂O₃ support (blue-shaded) with typical MFI layer morphology²⁵. Negative helium leakage tests (results not shown here) demonstrate that the as-prepared membrane is rather crack-free, a crucial feature for effective separations. Pore sizes in the range of 0.57 to 0.61 nm (Figure 5.1d, brown line) indicate the formation of the MFI structure and confirmed by X-ray diffraction (Figure 5.2). The Al₂O₃ support (blue line) has pores mostly larger than 40 nm in diameter.

The employed sensor is smaller than a match head (Figure 5.1e) and can be combined modularly with the membrane. It features a highly porous chemoresistive sensing film (d = 500 μ m) at its center (Figure 5.1f,g). The open structure allows analytes to rapidly diffuse in the sensing film and interact with the large surface area enabling detection even of trace-level concentrations. In fact, such nanostructured Pd-doped SnO₂ sensors are highly sensitive and can detect formaldehyde down to 3 ppb (at 90% RH) but without membrane they are not selective.¹⁰



Figure 5.2: (a) XRD patterns of zeolite powder (top), membrane (middle) and Al_2O_3 pellet (bottom) with a magnification of $2\theta = 5 - 25^\circ$ shown in (b). For the membrane, MFI peaks indicate the hydrothermally grown zeolite film on top of the Al_2O_3 pellet.

5.3.2 Zeolite membrane turn sensor formaldehyde selective

The effect of the MFI/Al₂O₃ membrane on gas sensing is evaluated using seven analytes that cover a variety of chemical groups and kinetic diameters²⁶⁻²⁸: NH₃ (3.3 Å), formaldehyde (3.7 Å), methanol (3.8 Å), ethanol (4.3 Å), acetone (4.7 Å), isoprene (5.5 Å) and 1,3,5-triisopropylbenzene (TIPB, 8.4 Å). Most of these analytes are relevant for breath analysis and indoor air monitoring while TIPB represents molecules larger than the MFI pore size.

Figure 5.3a shows the change in film resistance of Pd-doped SnO_2 *without membrane* upon exposure to 1 ppm of individual analytes in air with 50% RH. When introducing an analyte, the sensor resistance drops rapidly. In specific for formaldehyde (green line), it decreases from 253 to 25.7 k Ω corresponding to a normalized response (S_{FA}) of 8.8 (Figure 5.3b). The rather weak formaldehyde selectivities (S_{FA}/S_{analyte}), for instance to isoprene (1.4) and ethanol (3), demonstrate the non-specific character of the Pd-doped SnO_2 sensor alone. In other words, this sensor *cannot* detect formaldehyde *selectively* in a gas mixture since it is not possible to distinguish it from other gases consistent with literature¹⁰.



Figure 5.3: (a) Film resistance of a Pd-doped SnO_2 sensor (without membrane) upon exposure to 1 ppm of NH_3 (orange), acetone (red), methanol (light blue), TIPB (black), ethanol (blue), isoprene (purple) and formaldehyde (green) at 50% RH. The sensor detects well all these analytes rendering it rather non-selective, as indicated by the calculated responses in (b). Introducing the MFI/Al_2O_3 membrane turns the device FA-selective (c, d). Note the different scale of the ordinate in (b) and (d). Error bars indicate the response standard deviations of three identical sensors without (b) and with three identical membranes (d) being \pm 5 and 11% for formaldehyde, respectively.

Now, when installing the MFI/Al₂O₃ membrane and exposing the device to the individual analytes again, *only* formaldehyde is detected (Figure 5.3c,d). More specifically, the response to formaldehyde is

decreased to 1.85 while the responses to all other analytes are suppressed almost completely. That way, the formaldehyde selectivity to acetone is improved to more than 100 and that to NH₃, isoprene, ethanol, methanol and TIPB is even more than 1000, much higher than without membrane and considerably better than state-of-the-art formaldehyde detectors (Table 1). These include various chemoresistive gas sensors based on metal-oxides (e.g. Ag-doped LaFeO₃²⁹, TiO₂ nanotubes³⁰) and metal-organic frameworks (e.g ZIF-67³¹) that had been optimized particularly for formaldehyde. Alternatively, formaldehyde can be detected also by optical sensors including the commercially available FP-30 (RKI Instruments)³² but also this detector exhibits weaker selectivity to methanol and acetone (Table 1). Only fiber-optic devices show comparable performance³³. These, however, are more complex and expensive than the present device.

chemoresistive	Туре	Material	Formaldehyde selectivity S _{FA} /S _x [-]				Pof
			Ammonia	Ethanol	Acetone	Isoprene	1761
	MOx sensor+ membrane	Pd:SnO ₂ + MFI/Al ₂ O ₃	>1000	>1000	>100	>1000	This work
	MOx sensor only	Pd:SnO ₂	27	2.3	9	1.4	This work
		Ag:LaFeO₃	35	27	50	-	28
		TiO ₂ nanotubes	12	57 ^a	-	-	29
	ZIF sensor	ZIF-67	43	2 ^b	2	-	30
	Coated sensor	ZIF-8 coated ZnO	5	7	11	-	17
optical	RKI Instr. FP-30	Colorimetric sensor	-	high	8	-	31,32
	Fiber-optic	NADH flow cell	-	high	high	-	32

Table 5.1: Selectivity of formaldehyde detectors

^alinearly interpolated to same concentrations ^bselectivity to methanol

5.3.3 Separation mechanism of membrane

Based on the sensor results (Figure 5.3b,d), only formaldehyde seems to pass through the microporous MFI/Al₂O₃ membrane while all other analytes are held back at this low concentration (1 ppm). TIPB is filtered out effectively as its molecular size is larger than the MFI pore diameter (Figure 5.1d). This *size cut-off* confirms that the membrane is rather defect-free, a highly relevant feature for selective gas sensing from complex gas mixtures. Human breath and indoor air contain a myriad of large molecules which should be sieved out similarly effective as the TIPB model substance. Such a size cut-off is not possible with zeolite packed bed filters that have been combined also with gas sensors¹⁹.

For an effective size cut-off, thermal decoupling of the membrane from the heated sensor (400 C°) is crucial, as larger molecules could be cracked at acidic sites of the external zeolite surface¹³. This is ensured here by the modular arrangement. Furthermore, such catalytic effects may compromise size selectivity, for instance, in microporous layers or coatings directly applied on heated sensing films. In fact, ZIF-8 coatings on ZnO sensors operated at 300 °C showed poor formaldehyde selectivity even for larger analytes than the ZIF-8 pore size (3.4Å) including acetone and ethanol³⁴. Additionally, reactions can occur also for molecules smaller than the zeolite pore size at acidic sites inside the zeolite framework.¹² This can alter the composition of the gas mixture from the original sample. Thus, species not representing the sample reach the sensor, providing inaccurate results.

Surprisingly, also analytes smaller than the zeolite size cut-off (isoprene, NH₃, acetone, ethanol and methanol) did not lead to detectable sensor responses at a feed concentration of 1 ppm (Figure 5.3c,d). This *chemical separation* is attributed to different *sorption* and *diffusion properties* of the analytes in the MFI framework. The concentration

difference across the membrane governs the transport of small molecules (below the size cut-off) and higher analyte concentrations should increase permeation. In fact when exposing the membrane to methanol and acetone at 10 ppm and 50% RH (Appendix Figure C.3), small responses of 0.017 and 0.006 are obtained, respectively, in agreement with literature¹⁵. Nevertheless, both responses are still two orders of magnitude smaller than that to 1 ppm of formaldehyde (1.85, Figure 5.3d) emphasizing the outstanding separation performance of the membrane. Increasing the TIPB feed concentration to 10 ppm did not change the response, confirming effective molecular sieving and membrane integrity.

5.3.4 Formaldehyde monitoring and lower detection limit

Figure 5.4a shows the sensor responses for 0 - 1000 ppb of formaldehyde at 50% and 90% RH (triangles). The sensor responses increase continuously with increasing formaldehyde concentration and this allows to identify it clearly over the entire range. In human breath³⁵ or indoor air³⁶, formaldehyde occurs typically at concentrations below 100 ppb while other analytes may be present at much higher level (e.g. 833 ppb is the mean NH₃ concentration in breath³⁷). Most notably, when simulating such a situation by introducing different quantities of formaldehyde along with NH₃, acetone, isoprene and ethanol each at 1000 ppb, the calibration curve (squares) *does not change* even at 30 ppb of formaldehyde. This emphasizes the outstanding separation properties of the membrane that are crucial for reliable breath diagnostics and indoor air monitoring. Especially at these low formaldehyde concentrations, such membranes outperform E-noses that suffer from elevated estimation errors of 25% at 30 ppb while they perform similarly well at higher concentrations (e.g. 6% at 180 ppb) in comparable simulated breath mixtures¹⁰.



Figure 5.4: (a) Membrane-sensor assembly responses to breath-relevant formaldehyde (0 - 1000 ppb) at 50% and 90% RH (triangles). As demonstrated at 50% RH, the responses do not change even when introducing simultaneously 1000 ppb of NH_3 , acetone, isoprene and EtOH (squares). This highlights the excellent formaldehyde selectivity of the microporous membrane-sensor assembly. (b) Sensor film resistance upon exposure to 100, 70, 60 and 30 ppb of formaldehyde at 90% RH. These ultra-low analyte concentrations are detected reproducibly with high signal-to-noise ratio (> 70) distinguishing them clearly.

Humidity levels in exhaled breath typically range from 89 - 97 % RH³⁸. When increasing RH to 90%, the slope of the sensor response (Figure 5.4a) decreases indicating reduced sensitivity that is typical for SnO₂-based sensors³⁹. So water vapor seems to permeate through the membrane, as had been observed even for hydrophobic MFI²⁵. Nevertheless, the detector sensitivity is still sufficient to reliably detect formaldehyde levels below 100 ppb. In fact, when exposing the membrane-sensor assembly to 100, 70, 60 and 30 ppb of formaldehyde at 90% RH (Figure 5.4b), these concentrations are detected clearly with a high signal-to-noise ratio, SNR, (> 70). The extrapolated limit of detection (LOD) is at 0.2 ppb (at SNR = 1). This is comparable to identical Pd-doped SnO_2 without membrane (LOD = 0.1 ppb),¹⁰ indicating little impact of the membrane on LOD, and much better than ZIF-coated ZnO (5.6 ppm at 50 - 60% RH)³⁴. Additionally, this system features remarkable formaldehyde resolution and concentrations of 60 to 70 ppb can be distinguished clearly. That way, and most importantly, this device could discriminate between median breath formaldehyde levels of lung cancer patients (83 ppb) and healthy ones (48 ppb)³⁵ when incorporated into a portable breath sampler⁶. Furthermore, it can identify situations where formaldehyde exceeds the recommended indoor air limit of 100 ppb³⁶ and the eye irritation threshold at 500 ppb³⁶ to avoid potential cancer risks and sensory impairment.

Another important requirement for breath analyzers is repeatable applicability. As shown in Figure 5.4b, the sensor always fully recovers the initial baseline after exposure indicating *reversible* formaldehyde permeation through the membrane and interaction with the sensing structure without any observable deactivation. The sensor responses are also stable and well reproducible. In fact, when exposing the sensor twice to 60 ppb of formaldehyde, the same resistance is achieved (dashed line, Figure 5.4b).

5.4 Conclusions

In conclusion, combining nanostructured chemoresistive gas sensors with microporous membranes can result in highly sensitive detectors with *unprecedented selectivity*. Here, this was demonstrated by placing a zeolite MFI/Al₂O₃ membrane upstream a non-specific Pd-doped SnO₂ sensor exhibiting superior formaldehyde selectivity at relevant concentrations over existing devices (Table 1). At the same time, the sensor's high sensitivity was maintained to detect formaldehyde even down to 30 ppb at 50 and 90 % relative humidity, making it especially appealing for breath analysis and indoor air quality monitoring. Both, membrane and sensor can be incorporated easily into portable devices due to their compact and modular design.

In a broader sense, applying microporous membranes could represent a paradigm change in current gas sensor development. Most gas sensor types, such as chemoresistive metal oxides, optical photoionization detectors and mass-sensitive quartz microbalances, suffer from weak selectivity that hinders their reliable application in breath analysis and air quality monitoring. In case of chemoresistive sensors, selectivity had been tuned so far primarily by engineering *surface reactivity*, but high selectivity was observed only for a few analyte-material combinations so far. Microporous membranes introduce the capability of *molecular size selection* and chemical separation based on adsorption and diffusion properties providing much greater flexibility in selectivity optimization. A broad variety of microporous zeolite and metal-organic frameworks with widely tunable separation properties is available for such membranes and can be combined with any type of detector due to the modular arrangement. Thus, this membrane-sensor device strategy can be extended readily to other target compounds. This could facilitate a new generation of portable breath

analyzers or indoor air monitors featuring unprecedented sensitivity and selectivity.

5.5 References

- [1] T. H. Risby and S. F. Solga, Current status of clinical breath analysis, *Appl. Phys. B*, **2006**, 85, 421-426.
- G. Peng, U. Tisch, O. Adams, M. Hakim, N. Shehada, Y. Y. Broza, S. Billan, R. Abdah-Bortnyak, A. Kuten and H. Haick, Diagnosing lung cancer in exhaled breath using gold nanoparticles, *Nat. Nanotech.*, 2009, 4, 669-673.
- [3] A. Tricoli and S. E. Pratsinis, Dispersed nanoelectrode devices, *Nat. Nanotech.*, **2010**, 5, 54-60.
- [4] C. Hagleitner, A. Hierlemann, D. Lange, A. Kummer, N. Kerness, O. Brand and H. Baltes, Smart single-chip gas sensor microsystem, *Nature*, 2001, 414, 293-296.
- [5] S. Steinhauer, A. Chapelle, P. Menini and M. Sowwan, Local CuO Nanowire Growth on Microhotplates: In Situ Electrical Measurements and Gas Sensing Application, *ACS Sens.*, **2016**, 1, 503-507.
- [6] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, J. Breath Res., 2015, 9, 047101.
- [7] A. T. Güntner, N. J. Pineau, D. Chie, F. Krumeich and S. E. Pratsinis, Selective sensing of isoprene by Ti-doped ZnO for breath diagnostics, *J. Mater. Chem. B*, 2016, 4, 5358-5366.
- [8] A. T. Güntner, M. Righettoni and S. E. Pratsinis, Selective sensing of NH₃ by Si-doped α-MoO₃ for breath analysis, *Sens. Actuators B*, 2016, 223, 266-273.

- K. Persaud and G. Dodd, Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose, *Nature*, 1982, 299, 352-355.
- [10] A. T. Güntner, V. Koren, K. Chikkadi, M. Righettoni and S. E. Pratsinis, E-Nose sensing of low-ppb formaldehyde in gas mixtures at high relative humidity for breath screening of lung cancer?, ACS Sens., 2016, 1, 528-535.
- [11] G. Korotcenkov, Handbook of gas sensor materials, Springer, 2013.
- [12] B. Smit and T. L. Maesen, Towards a molecular understanding of shape selectivity, *Nature*, **2008**, 451, 671-678.
- [13] M. Choi, K. Na, J. Kim, Y. Sakamoto, O. Terasaki and R. Ryoo, Stable single-unit-cell nanosheets of zeolite MFI as active and longlived catalysts, *Nature*, 2009, 461, 246-249.
- [14] M. Y. Jeon, D. Kim, P. Kumar, P. S. Lee, N. Rangnekar, P. Bai, M. Shete, B. Elyassi, H. S. Lee, K. Narasimharao, et al., Ultra-selective high-flux membranes from directly synthesized zeolite nanosheets, *Nature*, 2017, 543, 690-694.
- [15] S. Aguado, A. C. Polo, M. P. Bernal, J. Coronas and J. Santamaría, Removal of pollutants from indoor air using zeolite membranes, J. Membr. Sci., 2004, 240, 159-166.
- [16] E. M. Flanigen, J. Bennett, R. Grose, J. Cohen, R. Patton and R. Kirchner, Silicalite, a new hydrophobic crystalline silica molecular sieve, *Nature*, **1978**, 271, 512-516.
- [17] K. Varoon, X. Zhang, B. Elyassi, D. D. Brewer, M. Gettel, S. Kumar, J. A. Lee, S. Maheshwari, A. Mittal, C.-Y. Sung, et al., Dispersible exfoliated zeolite nanosheets and their application as a selective membrane, *Science*, 2011, 334, 72-75.
- [18] D. L. Gin and R. D. Noble, Designing the Next Generation of Chemical Separation Membranes, *Science*, 2011, 332, 674-676.

- [19] O. Hugon, M. Sauvan, P. Benech, C. Pijolat and F. Lefebvre, Gas separation with a zeolite filter, application to the selectivity enhancement of chemical sensors, *Sens. Actuators B*, 2000, 67, 235-243.
- [20] M. Hakim, Y. Y. Broza, O. Barash, N. Peled, M. Phillips, A. Amann and H. Haick, Volatile organic compounds of lung cancer and possible biochemical pathways, *Chem. Rev.*, **2012**, 112, 5949-5966.
- [21] International Agency for Research on Cancer, *IARC classifies* formaldehyde as carcinogenic to humans, IARC, Lyon, 2004.
- [22] Z. A. E. P. Vroon, K. Keizer, M. J. Gilde, H. Verweij and A. J. Burggraaf, Transport properties of alkanes through ceramic thin zeolite MFI membranes, *J. Membr. Sci.*, **1996**, 113, 293-300.
- [23] J. Dong, K. Wegner and Y. S. Lin, Synthesis of submicron polycrystalline MFI zeolite films on porous ceramic supports, J. Membr. Sci., 1998, 148, 233-241.
- [24] L. M\u00e4dler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, *Sens. Actuators B*, **2006**, 114, 283-295.
- [25] H. Zhou, D. Korelskiy, E. Sjöberg and J. Hedlund, Ultrathin hydrophobic MFI membranes, *Micropor. Mesopor. Mat.*, 2014, 192, 76-81.
- [26] M. Van Leeuwen, Derivation of Stockmayer potential parameters for polar fluids, *Fluid Phase Equilib.*, **1994**, 99, 1-18.
- [27] M. Arruebo, J. L. Falconer and R. D. Noble, Separation of binary C₅ and C₆ hydrocarbon mixtures through MFI zeolite membranes, J. *Membr. Sci.*, 2006, 269, 171-176.
- [28] E. McLeary, J. Jansen and F. Kapteijn, Zeolite based films, membranes and membrane reactors: Progress and prospects, *Micropor. Mesopor. Mat.*, 2006, 90, 198-220.

- [29] Y. Zhang, Q. Liu, J. Zhang, Q. Zhu and Z. Zhu, A highly sensitive and selective formaldehyde gas sensor using a molecular imprinting technique based on Ag-LaFeO₃, J. Mater. Chem. C, 2014, 2, 10067-10072.
- [30] S. Lin, D. Li, J. Wu, X. Li and S. A. Akbar, A selective room temperature formaldehyde gas sensor using TiO₂ nanotube arrays, *Sens. Actuators B*, 2011, 156, 505-509.
- [31] E.-X. Chen, H. Yang and J. Zhang, Zeolitic imidazolate framework as formaldehyde gas sensor, *Inorg. Chem.*, **2014**, 53, 5411-5413.
- [32] RKI Instruments, Technical Datasheet FP-30 Formaldehyde Detector, accessed 09/2016.
- [33] H. Kudo, Y. Suzuki, T. Gessei, D. Takahashi, T. Arakawa and K. Mitsubayashi, Biochemical gas sensor (bio-sniffer) for ultrahigh-sensitive gaseous formaldehyde monitoring, *Biosens. Bioelectron.*, 2010, 26, 854-858.
- [34] H. Tian, H. Fan, M. Li and L. Ma, Zeolitic imidazolate framework coated ZnO nanorods as molecular sieving to improve selectivity of formaldehyde gas sensor, ACS Sens., 2016, 1, 243-250.
- [35] P. Fuchs, C. Loeseken, J. K. Schubert and W. Miekisch, Breath gas aldehydes as biomarkers of lung cancer, *Int. J. Cancer*, 2010, 126, 2663-2670.
- [36] R. Golden, Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards, *Crit. Rev. Toxicol.*, 2011, 41, 672-721.
- [37] C. Turner, P. Španěl and D. Smith, A longitudinal study of ammonia, acetone and propanol in the exhaled breath of 30 subjects using selected ion flow tube mass spectrometry, SIFT-MS, *Physiol. Meas.*, 2006, 27, 321.
- [38] L. Ferrus, H. Guenard, G. Vardon and P. Varene, Respiratory water loss, *Respir. Physiol.*, **1980**, 39, 367-381.

SnO₂ sensors in the presence of humidity, *J. Phys.-Condes. Matter*, **2003**, 15, R813-R839.

Body fat burn monitoring from exhaled acetone with Si-doped WO₃ sensing nanoparticles

Abstract Obesity is a global health threat on the rise and its prevalence continues to grow. Yet suitable biomedical sensors to monitor the body fat burn rates in situ to guide physical activity or dietary interventions toward efficient weight loss are missing. Here, we introduce a compact and inexpensive breath acetone sensor based on Si-doped WO₃ nanoparticles that can accurately follow body fat burn rates in *real-time*. We tested this sensor on 20 volunteers during exercise and rest and measured their individual breath acetone concentrations in good agreement to bench-top proton transfer reaction time-of-flight mass spectrometry (PTR-TOF-MS). During exercise, this sensor reveals clearly the onset and progression of increasing breath acetone levels that indicate intensified body fat metabolism, as validated by parallel venous blood β -hydroxybutyrate (BOHB) measurements. 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 dieting as well.

6.1 Introduction

Worldwide 15% of women and 11% of men were obese (BMI \ge 30 kg m⁻²) in 2014¹ with increasing numbers in most countries². Unfortunately, conventional technologies either fail to indicate body fat burn rates *in situ* to guide physical activity and dietary interventions or are too costly for widespread application (e.g. indirect calorimetry). Analyzing volatile organics in human breath opens exciting new avenues for the next generation of health monitoring devices.³ In particular, measuring exhaled acetone, a volatile byproduct of lipolysis⁴, with a portable device could enable such personal body fat burn monitors⁵. With breath analysis being non-invasive, user-friendly (similar to sweat analysis⁶) and always accessible,⁷ it might be ideal for easy and routine application in gyms or at home.

Breath acetone had been measured already with gas chromatography-⁸ and mass spectrometer-based techniques⁹⁻¹², chemical adsorption columns¹³ and electronic noses¹⁴. However, these are expensive with limited portability⁸⁻¹², for single use only with long response time (> 5 min)¹³ or just inaccurate¹⁴, thus hardly suitable for routine measurements with personal monitors. Modern chemoresistive gas sensors are promising candidates for personal breath analyzers due to their extremely compact design¹⁵, high gas sensitivity when nanostructured^{16,17} and current use in breath analysis (e.g. hemodialysis monitoring¹⁸). However, the challenge remains to design the sensing material selective to acetone for reliable detection in the complex matrix of human breath (872 compounds identified previously¹⁹).

Here, we report a portable breath acetone sensor based on Si-doped WO_3 nanoparticles to monitor body fat burn rates in real-time during exercise and rest. We evaluated this sensor in combination with a tailor-made sampler for reproducible breath extraction on 20 volunteers and

measured their individual breath acetone profiles. These results were closely compared to simultaneously measured breath analysis by state-of-the-art proton transfer reaction time-of-flight mass spectrometry (PTR-TOF-MS) to assess the sensors accuracy and parallel venous blood β -hydroxybutyrate (BOHB) to confirm the relation to fat metabolism activity.

6.2 Experimental

6.2.1 Acetone sensor fabrication and film characterization

The Si-doped (10 mol%) ε -WO₃ nanoparticles were prepared by FSP deposited²⁰ onto Al₂O₃ substrates with interdigitated directly and electrodes.²¹ The FSP precursor solution consisted of ammonium metatungstate hydrate (Honeywell, purity \geq 99%) and hexamethyl disiloxane (Sigma Aldrich, purity \geq 98%) to obtain the nominal Si content. This was diluted by a 1:1 mixture of ethanol (Sigma Aldrich, purity \geq 99.8%) and diethylene glycol monobutyl ether (Sigma Aldrich, purity \geq 98%) to achieve a final metal (W and Si) concentration of 0.2 M. This precursor is fed at 5 mL min⁻¹ through a FSP nozzle and dispersed (1.5 bar pressure drop) by 5 L min⁻¹ oxygen to a fine spray ignited by a ring-shaped flame of premixed methane / oxygen (1.25 / 3.2 L min⁻¹) while additional sheath oxygen was supplied at 5 L min⁻¹. The Al₂O₃ substrates featured dimensions of 15 x 13 x 0.5 mm and had a set of interdigitated electrodes (spacing 350 µm) and a Pt temperature resistance detector (RTD) on the front side. A Pt heater to control the temperature was placed on the back. The morphology of the sensing films was characterized by scanning electron microscope (SEM) with a Hitachi FE-SEM 4000 operated at 5 kV. To investigate the film's cross-section, the sensors were split prior to the measurement.

6.2.2 Breath sampler design

The sampler is illustrated in Figure 6.1d. It comprised a disposable and sterile mouthpiece (EnviTeC-Wismar) connected to an open-ended sampler tube with an inner diameter of 25 mm and a length of 375 mm to sample and buffer²² end-tidal breath. A flow restrictor (1.4 mm orifice) was installed inside the sampler tube just behind the mouthpiece and the relative airway pressure ($p_{mouth} - p_{surrounding}$) was measured with a differential pressure sensor (SDP, Sensirion) at the orifice. A transfer line ($d_i = 6$ mm) was connected to the sampler tube to extract breath sample for the acetone sensor and PTR-TOF-MS. A CO₂ sensor (Capnostat 5, Respironics) was placed in the transfer line to monitor the breath portions. All surfaces in contact with the breath were either disposable (mouthpiece) or made of inert Teflon and heated to 60 °C to avoid analyte adsorption and water condensation to minimize cross-contamination.

6.2.3 Breath and blood analysis

Sampled breath was analyzed in real-time with the acetone sensor and a PTR-TOF-MS simultaneously. Therefore, the acetone sensor was mounted on a Macor holder, installed in a Teflon chamber²³ and connected to the breath sampler via the transfer line, as shown in Figure 6.1d. The sensor was fed with a constant flow of 130 mL min⁻¹ by a vane pump (SP 135 FZ, Schwarzer Precision) connected to the sensor chamber's exhaust. A DC source (R&S HMC8043) was applied to heat the acetone sensor to its optimal temperature of 350 °C²³ while that was monitored continuously by the substrate's RTD. Sensing film (ohmic) resistances were measured and recorded with a multimeter (Keithley 2700). The PTR-TOF-MS 1000 (Ionicon Analytik, Austria) was fed from the sensor transfer line with sample extraction just before the acetone sensor (Figure 1d). The ionization

conditions were 600 V drift voltage, 60 °C drift temperature and 2.3 mbar drift pressure. Acetone concentrations were determined in the H_3O^+ mode by measuring the counts per second at a mass-to-charge ratio of 59.049²⁴ and comparing them to calibration curves determined routinely before the breath tests with a calibrated acetone gas standard (10 ppm in synth. air, Pan Gas 5.0). Venous blood samples were analyzed for β -hydroxybutyrate concentration by the Institute of Clinical Chemistry of the University Hospital Zurich.

6.2.4 Study design

A cohort of 20 volunteers (13 male and 7 female) with an age of 20 - 33 years participated in this study. All were in a healthy condition and had a body mass index between 18.3 and 27.7 kg m^{-2} (for detailed information see Appendix Table D.1). Each subject had been informed about the proceeding and signed a consent form prior to the tests. This study had been approved by the Kantonale Ethikkommission Zürich. The volunteers were asked in advance to fast for 12 h, not to brush their teeth nor use mouthwash for 2 h and stay abstinent from alcoholic beverages for 24 h before and during the experiment to avoid exogenous interferences. Each volunteer was tested twice on different days. The first test (denoted as *exercise*) consisted of 3 x 30 min initial moderate physical activity, with 15 min breaks in between for breath and venous blood sampling, followed by 3 hours of rest. The second test (denoted as *control*) followed the same protocol, however, this time without initial exercise but staying at rest throughout the entire testing course. Physical activity was performed on a bicycle Ergometer (E5, Kettler) with power-independent pedal speed and heart rate control with a pulse belt (T34, Polar). The workload was adapted automatically by the ergometer to maintain a heart rate at $63\%^{25}$ of the maximum one (HR_{max}) at
60 - 80 revolutions per minute. HR_{max} was approximated for men with $HR_{max} = 223 - 0.9$ age (in years) and for women with $HR_{max} = 226$ - age. Breath was sampled in total seven times: just before physical activity, after each 30 min of physical activity and thereafter every 60 min during rest. Venous blood samples were taken three times: before the physical activity, after the physical activity and at the end of the test.

6.3 Results and discussion

6.3.1 Breath acetone sensor design

The employed compact and inexpensive sensor features a thin Si-doped WO_3 sensing film on top of interdigitated electrodes (Figure 6.1a). Such films are highly porous (Figure 6.1b) consisting of a fine structures of Sidoped WO₃ nanoparticles (Figure 6.1c), typical for such flame-made layers^{26,27}. The open structure of the sensing film allows gas molecules to diffuse rapidly through the film for fast response and recovery times, suitable for breath analysis in real-time²³. Also, it provides large surface area to sense acetone even at lowest concentrations (e.g. 20 ppb²³), sufficient for breath acetone detection with levels typically above 150 ppb^{11} . semiconductive metal-oxide In principle, such nanoparticles are chemoresistive-type gas sensors. In other words, analytes (e.g. acetone) interact with surface species of the metal oxide modulating the film resistance and resulting in a detectable sensor response.²⁸ In specific for WO_3 , analyte interaction with lattice oxygen at the surface may dominate²⁹. Most remarkably, since these surface interactions are reversible, such sensors are suitable for multiple²³ and even continuous breath analyses.



Figure 6.1: Breath analyzer for non-invasive body fat burn monitoring. (a) Compact acetone sensor mounted on a Macor holder. (b) Scanning electron microscopy exhibits the highly porous morphology of the sensing film (crosssection) (c) formed by aggregated, acetone-selective Si-doped WO₃ nanoparticles (NPs). (d) Breath analyzer combining the acetone sensor with a sampler to extract breath in a standardized fashion. The sampler comprises a tube to capture and buffer end-tidal breath, a pressure sensor to monitor the relative airway pressure and a CO₂ sensor. Parallel PTR-TOF-MS analysis just before the acetone sensor is performed for cross-validation. (e) Breath analyzer in operation: the subject exhales into the sampler tube and receives prompt visual feed-back on airway pressure, duration and acetone sensor analysis. (f) Sensor signals for relative airway pressure (black line) and CO₂ (red line) for three 30 s exhalations (gray-shaded) of a subject. The target airway pressure of 980 Pa (dashed line) is maintained well, corresponding to a flow of 50 mL s⁻¹. (g)

Acetone sensor responses (black line) and concentrations from PTR-TOF-MS (blue line). Both provide comparable acetone measurement in real-time. Note that sensor response is defined as: R_{air}/R_{breath} -1 with R_{air} being the sensor film resistance in surrounding air and R_{breath} when exposed to the breath sample.

Given the complexity of breath, a key challenge in sensor development is sufficient selectivity to acetone to ensure an accurate measurement. Here, we address this by applying ferroelectric ε -WO₃ exhibiting high acetone selectivity³⁰. This is probably due to strong interaction between the spontaneous electric dipole moment of ε -WO₃ with the high dipole moment of acetone³⁰. The metastable ε -WO₃ is stabilized by Si-doping (10 mol%)³¹. Such sensors had been evaluated already in simulated breath mixtures to detect various acetone concentrations²³ and showed promising results in offline³² and online²³ breath tests with a portable analyzer³³.

6.3.2 Breath sampling and analysis strategy

Reliable acetone analysis requires standardized breath sampling since different breathing maneuvers and sample volume affect acetone concentration.⁵ Therefore, a novel sampler was designed (Figure 6.1d,e, please see Experimental) to extract reproducible end-tidal breath in a monitored fashion (by relative airway pressure and CO₂ concentration) with minimal effort for the subject. While early breath involves air from the mouth and upper airways (anatomic dead space), most relevant and highest acetone levels occur in the later portions from the bronchi and pulmonary alveoli (end-tidal breath) containing chemical information about blood composition (including metabolic products) due to the gas exchange in the lung.³⁴ In principle, complete breath is exhaled through an open-ended sampler tube. After exhalation, only the end-tidal portion remains inside the tube and is fed to the sensor for prolonged exposure, as can be evaluated from the CO₂ profiles (Figure 6.1f, red line) of three consecutive exhalations

(each 30 s) of a subject: During exhalation, the CO₂ concentration increases rapidly until it reaches a maximum at 6.2 - 6.4%, indicative of end-tidal breath $(CO_2 > 3\%)^{35}$. Most importantly, this portion is buffered for an additional 20 s after exhalation before the CO₂ level declines rapidly and stabilizes again at the initial baseline indicating fast and complete refreshment or regeneration of the sampler tube.

Figure 6.1g shows the corresponding acetone sensor responses (black line) and concentrations measured by PTR-TOF-MS (blue line). Both instruments respond immediately with reproducible results for the three breath samples. In specific, the acetone sensor response increases rapidly and reaches each time a maximum at a response of ~2 during the prolonged exposure to end-tidal breath. This corresponds to an acetone level of ~960 ppb, as measured by the PTR-TOF-MS, and it is within typical daily variation¹¹. While the sensor features slower response times than the PTR-TOF-MS, it is still sufficiently fast to detect the acetone reliably with the present sampler. The sensor shows also higher signal-to-noise-ratio than PTR-TOF-MS, a favorable feature for signal analysis. After exposure, the sensor and PTR-TOF-MS always recover the initial baseline, similar to CO₂ (Figure 6.1f, red line), and are ready for re-use.

6.3.3 Individual body fat burn monitoring during exercise and rest

The sampler-sensor system was applied to monitor the breath acetone dynamics of 20 volunteers during exercise and post-exercise rest. Therefore, all subjects underwent exercise with initial three times 30 min cycling on an ergometer at moderate intensity (Figure 6.2a,b, please see Experimental) to stimulate their body fat metabolism followed by a 3 h rest. Prior to and throughout the testing course, the volunteers have been fasting to minimize the influence of food intake. The corresponding breath acetone profiles of four representative volunteers (for physiological data of all subjects, please see Appendix Table D.1) are shown in Figure 6.2c. Note that breath acetone is indicated as relative change from the initial value (at t = 0) to evaluate only the effect of the exercise. That way, also a comparison between subjects is easier, as their initial acetone concentrations may vary significantly due to biological variability¹¹.

In a typical case (e.g. subject #18, red diamonds), breath acetone increases only little during exercise but triples during the post-exercise rest. Increasing breath acetone concentrations during and after exercise have been observed also in other studies (e.g. during cycling⁸ and walking¹⁰) and should reflect enhanced body fat metabolism with acetone being a byproduct of lipolysis⁴. Thus for subject #18, it seems that the initial exercise stimulated the body fat metabolism that becomes most pronounced after the exercise. To confirm this, venous blood β -hydroxybutyrate (BOHB) is analyzed simultaneously, as a marker for body fat metabolism⁵ (Figure 6.2d). Remarkably, it shows the same dynamic response supporting that the present breath acetone sensor follows indeed the body fat metabolism but, most importantly, in a *non-invasive* manner.

Individual body fat burn rates may differ between humans due to usual biological variability (including different fitness). Nevertheless, the sensor should recognize this correctly for *customized* feed-back. In fact, when comparing the individual exercise profiles of selected volunteers (Figure 6.2c), distinctly different breath acetone profiles are detected, again all in good agreement to BOHB dynamics (Figure 6.2d). For instance, subject #3 (blue circles) shows a steady breath acetone increase already during exercise with higher concentrations during the post-exercise rest, similar to #18 though at lower level.



Figure 6.2: Body fat burn monitoring during exercise and rest. Typical cycling power profiles (a) and heart frequency (b) of a subject when 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. Note that the load is adjusted automatically during cycling to keep the subject always at approx. 63% of the maximum heart rate. Symbols in (b) indicate breath (orange circles) and venous blood (green squares) sampling. c, Individual breath acetone changes (relative to initial value) measured by the sensor of representative subjects during the testing Corresponding venous blood β -hydroxybutyrate course. (d)(BOHB) concentrations that were sampled only 3 times instead of 7 as with breath (b) to minimize the discomfort for the volunteers.

On the other hand, the breath acetone of subject #9 (black squares) is hardly affected by exercise. In fact, it even decreases slightly during exercise. From these results, already a first feed-back can be provided to the subjects: while the work-out stimulated the body fat metabolism of subjects #3, 11 and 18 with highest rates during the post-exercise rest, it was not effective for subject #9. In a next step, this device could be used to guide the optimization of their training conditions (e.g. higher cycling intensity, type of exercise, etc.) to maximize the individual body fat metabolism.

For comparison, each volunteer was tested also another time following the same protocol, but without cycling (denoted as *control*). Figure 6.3a shows the average breath acetone change and variability of the 20 subjects when tested with exercise (red triangles) and as control (blue squares), respectively. While the volunteers responded in average with a breath acetone increase, especially after exercise, the sensor detects only a small breath acetone change towards the end of the measurement for *control*, probably due to the prolonged fasting of the volunteers¹² (see Appendix Figure D.1 for individual breath acetone). Both trends are again in agreement with the measured venous blood BOHB (Figure 6.3b).

To evaluate the correlation between the sensor-measured breath acetone and venous blood BOHB in more detail, Figure 6.3c shows the corresponding scatter plot of all data points. Breath acetone and BOHB correlate well with correlation coefficients of 0.82 (p < 0.05). This is quite comparable to other studies that found an average of 0.88 (there, however, for absolute concentrations)⁵. This provides further evidence that breath acetone is a suitable surrogate for body fat burn and the presented sensor monitors it non-invasively.

Finally to cross-validate the sensor's accuracy for breath acetone detection, all breath samples are analyzed simultaneously by PTR-TOF-MS. Figure 6.3d shows the scatter plot for the relative acetone change as measured by the sensor and PTR-TOF-MS for all 280 breath samples (for PTR-TOF-MS-measured acetone concentrations over time, please see Appendix Figure D.2). Both instruments correlate strongly (correlation coefficient 0.97, p < 0.05) and agree well without systematic bias and

3 Relative acetone change (sensor), а b 600 Venous BOHB, μmol L⁻¹ 400 2 Exercise 200 Control 0 Ó 300 100 200 100 200 300 Time, min Time, min Relative acetone change (sensor), Relative acetone change (sensor), d С 3 3 2 Pearson's r = 0.82 r = 0.97 ż 20 30 2 0 10 Relative venous BOHB change, -Relative acetone change (PTR-TOF-MS), -

sufficiently small limits of agreement, as indicated by additional Bland-Altman analysis³⁶ (please see Appendix Figure D.3).

Figure 6.3: Breath and venous blood data of 20 subjects. (a, b) Average acetone change measured by sensor (a) and venous blood β -hydroxybutyrate (BOHB) (b) concentrations during testing with 3 x 30 min initial exercise and 3 h rest (red triangles). For comparison, each subject is tested a second time as control (blue squares) following the same protocol, however then without exercise. Error bars indicate the standard deviations of 20 volunteers that are shown only half-sided for clearer visibility. (c, d) Scatter plots indicating the correlations between the relative acetone change measured by the sensor and venous blood BOHB (c) and the relative acetone change measured by the PTR-TOF-MS (d). Corresponding Pearson's (r) correlation coefficients along with fitted trend lines (dashed) and ideal line (solid in (d)) are indicated in the Figures as well.

Small sensor underprediction occurs only at higher acetone changes (compare in Figure 6.3d fitted (dashed) and ideal (solid) lines). As a result, our sensor reliably detects and monitors breath acetone. This is remarkable considering the sensor's compactness and low cost compared to the PTR- TOF-MS. At the same time, it is more accurate than chemical adsorption columns that are hand-held breath acetone detectors but for single-use¹³

6.4 Conclusions

A portable, easy-in-use and inexpensive breath acetone sensor was presented that can monitor *in situ* body fat burn dynamics during exercise and rest. It consists of an extremely porous film of flame-made Si-doped WO₃ nanoparticles for highly sensitive, selective and rapid breath acetone detection. To facilitate reproducible and reliable breath acetone analysis, a sampler that extracts and buffers the end-tidal fraction of breath for prolonged sensor exposure was crucial. When applied to 20 volunteers during exercise and rest, this sensor recognized and closely followed *individual* breath acetone concentrations, in good agreement to bench-top PTR-TOF-MS. Increasing breath acetone reflected intensified body fat metabolism, as confirmed by measured venous blood BOHB. Most remarkably, the strongest body fat burn was detected typically during a 3 h post-exercise rest. As a result, this compact breath analyzer is promising as body fat burn monitor for daily application at home or in gyms to provide immediate feed-back during exercise and dieting for more effective body fat loss.

6.5 References

- [1] Global status report on noncommunicable diseases 2014, World Health Organization, 2014.
- The GBD Obesity Collaborators, Health Effects of Overweight and Obesity in 195 Countries over 25 Years, N. Engl. J. Med., 2017, 377, 13-27.
- [3] K. Murphy, Journal, May 1, 2017.

- [4] M. P. Kalapos, On the mammalian acetone metabolism: from chemistry to clinical implications, BBA-Gen Subjects, 2003, 1621, 122-139.
- [5] J. C. Anderson, Measuring breath acetone for monitoring fat loss: Review, Obesity, 2015, 23, 2327-2334.
- [6] W. Gao, S. Emaminejad, H. Y. Y. Nyein, S. Challa, K. Chen, A. Peck,
 H. M. Fahad, H. Ota, H. Shiraki, D. Kiriya, et al., Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis, Nature, 2016, 529, 509-514.
- [7] T. H. Risby and S. F. Solga, Current status of clinical breath analysis, Appl. Phys. B, **2006**, 85, 421-426.
- [8] K. Yamai, T. Ohkuwa, H. Itoh, Y. Yamazaki and T. Tsuda, Influence of cycle exercise on acetone in expired air and skin gas, Redox Report, 2009, 14, 285-289.
- [9] J. King, A. Kupferthaler, K. Unterkofler, H. Koc, S. Teschl, G. Teschl, W. Miekisch, J. Schubert, H. Hinterhuber and A. Amann, Isoprene and acetone concentration profiles during exercise on an ergometer, J. Breath Res., 2009, 3, 027006.
- [10] D. Samudrala, G. Lammers, J. Mandon, L. Blanchet, T. H. Schreuder, M. T. Hopman, F. J. Harren, L. Tappy and S. M. Cristescu, Breath acetone to monitor life style interventions in field conditions: An exploratory study, Obesity, 2014, 22, 980-983.
- [11] C. Turner, P. Španěl and D. Smith, A longitudinal study of ammonia, acetone and propanol in the exhaled breath of 30 subjects using selected ion flow tube mass spectrometry, SIFT-MS, Physiol. Meas., 2006, 27, 321.
- [12] P. Spanel, K. Dryahina, A. Rejskova, T. W. E. Chippendale and D. Smith, Breath acetone concentration; biological variability and the influence of diet, Physiol. Meas., 2011, 32, N23-N31.

- [13] S. K. Kundu, J. A. Bruzek, R. Nair and A. M. Judilla, Breath acetone analyzer: diagnostic tool to monitor dietary fat loss, Clin. Chem., 1993, 39, 87-92.
- [14] T. Toyooka, S. Hiyama and Y. Yamada, A prototype portable breath acetone analyzer for monitoring fat loss, J. Breath Res., 2013, 7, 036005.
- [15] C. Hagleitner, A. Hierlemann, D. Lange, A. Kummer, N. Kerness, O. Brand and H. Baltes, Smart single-chip gas sensor microsystem, Nature, 2001, 414, 293-296.
- [16] A. T. Güntner, V. Koren, K. Chikkadi, M. Righettoni and S. E. Pratsinis, E-Nose sensing of low-ppb formaldehyde in gas mixtures at high relative humidity for breath screening of lung cancer?, ACS Sens., 2016, 1, 528-535.
- [17] S.-J. Choi, I. Lee, B.-H. Jang, D.-Y. Youn, W.-H. Ryu, C. O. Park and I.-D. Kim, Selective Diagnosis of Diabetes Using Pt-Functionalized WO3 Hemitube Networks As a Sensing Layer of Acetone in Exhaled Breath, Anal. Chem., 2013, 85, 1792-1796.
- [18] T. Hibbard, K. Crowley, F. Kelly, F. Ward, J. Holian, A. Watson and A. J. Killard, Point of Care Monitoring of Hemodialysis Patients with a Breath Ammonia Measurement Device Based on Printed Polyaniline Nanoparticle Sensors, Anal. Chem., 2013, 85, 12158-12165.
- [19] B. De Lacy Costello, A. Amann, H. Al-Kateb, C. Flynn, W. Filipiak,
 T. Khalid, D. Osborne and N. M. Ratcliffe, A review of the volatiles from the healthy human body, J. Breath Res., 2014, 8, 014001.
- [20] L. M\u00e4dler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, Sens. Actuators B, 2006, 114, 283-295.

- [21] M. Righettoni, A. Tricoli and S. E. Pratsinis, Thermally Stable, Silica-Doped ε-WO₃ for Sensing of Acetone in the Human Breath, Chem. Mater., 2010, 22, 3152-3157.
- [22] J. Herbig, T. Titzmann, J. Beauchamp, I. Kohl and A. Hansel, Buffered end-tidal (BET) sampling—a novel method for real-time breath-gas analysis, J. Breath Res., 2008, 2, 037008.
- [23] M. Righettoni, A. Tricoli, S. Gass, A. Schmid, A. Amann and S. E. Pratsinis, Breath acetone monitoring by portable Si:WO₃ gas sensors, Anal. Chim. Acta, 2012, 738, 69-75.
- [24] A. Jordan, S. Haidacher, G. Hanel, E. Hartungen, L. Märk, H. Seehauser, R. Schottkowsky, P. Sulzer and T. Märk, A high resolution and high sensitivity proton-transfer-reaction time-of-flight mass spectrometer (PTR-TOF-MS), Int. J. Mass spectrom., 2009, 286, 122-128.
- [25] D. P. Swain, K. S. Abernathy, C. S. Smith, S. J. Lee and S. A. Bunn, Target heart rates for the development of cardiorespiratory fitness, Med. Sci. Sports Exerc., 1994, 26, 112-116.
- [26] A. T. Güntner, N. J. Pineau, D. Chie, F. Krumeich and S. E. Pratsinis, Selective sensing of isoprene by Ti-doped ZnO for breath diagnostics, J. Mater. Chem. B, 2016, 4, 5358-5366.
- [27] A. T. Güntner, M. Righettoni and S. E. Pratsinis, Selective sensing of NH₃ by Si-doped α-MoO₃ for breath analysis, Sens. Actuators B, 2016, 223, 266-273.
- [28] N. Barsan and U. Weimar, Conduction Model of Metal Oxide Gas Sensors, J. Electroceram., 2001, 7, 143-167.
- [29] A. Staerz, C. Berthold, T. Russ, S. Wicker, U. Weimar and N. Barsan, The oxidizing effect of humidity on WO3 based sensors, Sens. Actuators B, 2016, 237, 54-58.

- [30] L. Wang, A. Teleki, S. E. Pratsinis and P. I. Gouma, Ferroelectric WO₃ Nanoparticles for Acetone Selective Detection, Chem. Mater., 2008, 20, 4794-4796.
- [31] M. Righettoni, A. Tricoli and S. E. Pratsinis, Si:WO₃ Sensors for Highly Selective Detection of Acetone for Easy Diagnosis of Diabetes by Breath Analysis, Anal. Chem., 2010, 82, 3581-3587.
- [32] M. Righettoni, A. Schmid, A. Amann and S. E. Pratsinis, Correlations between blood glucose and breath components from portable gas sensors and PTR-TOF-MS, J. Breath Res., 2013, 7, 037110.
- [33] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, J. Breath Res., 2015, 9, 047101.
- [34] J. C. Anderson, W. J. E. Lamm and M. P. Hlastala, Measuring airway exchange of endogenous acetone using a single-exhalation breathing maneuver, J. Appl. Physiol., 2006, 100, 880-889.
- [35] F. Di Francesco, C. Loccioni, M. Fioravanti, A. Russo, G. Pioggia, M. Ferro, I. Roehrer, S. Tabucchi and M. Onor, Implementation of Fowler's method for end-tidal air sampling, J. Breath Res., 2008, 2.
- [36] M. J. Bland and D. G. Altman, Statistical methods for assessing agreement between two methods of clinical measurement, The Lancet, 1986, 327, 307-310.

7

Research Recommendations

In this thesis, novel gas sensing materials, sensor arrays (E-noses) and filter membranes were presented with each of them featuring unprecedented selectivity. Further improvements can be achieved by systematically combining these components featuring all a modular design. For instance, incorporating ammonia-selective Si-doped MoO₃ (chapter 2) and acetoneselective Si-doped WO₃ sensors (chapter 6) into a SnO₂-based E-nose (chapter 4) increases its orthogonality/variance and this should improve estimation accuracy¹. Indeed, firsts tests with such an orthogonal E-nose in gas mixtures exhibit significantly reduced estimation error for acetone by 70% and ethanol by 65% (see Appendix A). That way, multiple components can be accurately and simultaneously detected in gas mixtures. Furthermore, this E-nose could be combined with a membrane that removes unwanted interferents from the gas mixture for improved E-nose robustness. For this purpose, over 180 zeolite structures are currently known² with widely tunable separation properties and these can be applied as needed. As a result, combining components and approaches developed in this theses provides great versatility to systematically develop selective sensors for target analytes.

While this thesis mainly focused on approaches to overcome selectivity issue of current chemoresistive gas sensors, other challenges remain that were addressed only partially and surely require further in-depth research. For instance, *power consumption* is a constraint of current metal-oxide sensors for their application in hand-held breath monitors and, in particular, for integration into smart phones. While the presented sensors feature already low enough power consumption for portable breath analyzers,³ it needs to be reduced further for battery-driven devices. State-of-the-art microfabrication technology offers solutions for improved thermal insulation of the heated sensing film by introducing closed or even suspended heater membranes.⁴ That way, power consumption for metal-oxide sensors are minimized typically to the low mW-range⁴ and operation with pulse-driven heating can reduce it even further.⁵

Alternatively, the operating temperature of the sensor could be reduced since heating power dominates the overall consumption. While metal-oxides typically require elevated operational temperature to enhance surface reactivity and lower the resistance, conductive polymers (e.g. polyaniline⁶) and carbon nanotubes⁷ possess promising sensitivity already at room temperature (RT). By combining these with the developed metal-oxides (e.g. as composite or functionalized), synergetic effects might allow to tune the selectivity of such RT sensors towards target breath markers. Despite the potential, however, current RT sensors suffer from slow response and recovery times that need to be improved significantly to become applicable for breath analysis.

While only few chemoresistive gas sensors had been tested on human breath so far⁸, it is a crucial step to evaluate the sensor's reliability and technical benefit. Important when performing breath tests is a standardized procedures for breath sampling and analysis.⁹ Otherwise, results remain non-repeatable, unreliable and inconclusive. Unfortunately, guidelines are available only for few breath compounds (e.g. NO¹⁰) while state-of-the-art knowledge about others is widely dispersed over the breath analysis literature and needs to be investigated carefully. Furthermore, rigorous cross-validation of the sensor with state-of-the-art analytical devices (e.g. PTR-TOF-MS) is necessary, similar as performed in chapter 6. Only that way, reliable detection of the target breath compound can be evidenced. Clinical studies require interdisciplinary collaboration between sensor engineers, breath analysis experts and clinicians and they are inevitable to ultimately realize breath sensors as medical or life science products.

7.1 References

- W. P. Carey, K. R. Beebe, E. Sanchez, P. Geladi and B. R. Kowalski, Chemometric analysis of multisensor arrays, *Sens. Actuators*, 1986, 9, 223-234.
- [2] B. Smit and T. L. Maesen, Towards a molecular understanding of shape selectivity, *Nature*, **2008**, 451, 671-678.
- [3] M. Righettoni, A. Ragnoni, A. T. Güntner, C. Loccioni, S. E. Pratsinis and T. H. Risby, Monitoring breath markers under controlled conditions, *J. Breath Res.*, 2015, 9, 047101.
- [4] I. Simon, N. Bârsan, M. Bauer and U. Weimar, Micromachined metal oxide gas sensors: opportunities to improve sensor performance, *Sens. Actuators B*, 2001, 73, 1-26.
- [5] K. Suematsu, Y. Shin, N. Ma, T. Oyama, M. Sasaki, M. Yuasa, T. Kida and K. Shimanoe, Pulse-Driven Micro Gas Sensor Fitted with Clustered Pd/SnO₂ Nanoparticles, *Anal. Chem.*, 2015, 87, 8407-8415.
- [6] T. Hibbard, K. Crowley, F. Kelly, F. Ward, J. Holian, A. Watson and A. J. Killard, Point of Care Monitoring of Hemodialysis Patients with a Breath Ammonia Measurement Device Based on Printed Polyaniline Nanoparticle Sensors, *Anal. Chem.*, 2013, 85, 12158-12165.
- [7] K. Chikkadi, M. Muoth, V. Maiwald, C. Roman and C. Hierold, Ultralow power operation of self-heated, suspended carbon nanotube gas sensors, *Appl. Phys. Lett.*, 2013, 103, 223109.

- [8] M. Righettoni, A. Amann and S. E. Pratsinis, Breath analysis by nanostructured metal oxides as chemo-resistive gas sensors, *Mater. Today*, 2015, 18, 163-171.
- [9] J. Herbig and J. Beauchamp, Towards standardization in the analysis of breath gas volatiles, *J. Breath Res.*, **2014**, 8, 037101.
- [10] American Thoracic Society and European Respiratory Society, ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, *Am. J. Respir. Crit. Care Med.*, **2005**, 171, 912-930.

Appendix A

E-nose 2.0: towards orthogonal sensor arrays for improved analyte estimation in mixtures

Abstract Breath analysis requires the accurate detection of multiple markers in the complex gas mixture of breath. While e-noses based on weakly selective sensors achieve combinatorial selectivity in gas mixtures, however, they often suffer from significant estimation errors to important breath tracers (e.g. acetone, ammonia and ethanol). This results mainly from the nearly collinear characteristics of the applied sensors typically possessing only diminutive selectivity differences to these analytes. Recent advances in material engineering, however, enable new sensing materials with promising selective performance. Here, a novel E-nose is presented that combines such dominantly selective sensors to an almost *orthogonal* array. In specific, the applied sensors are flame-made Si-doped WO₃, MoO₃ and SnO₂ sensors and they feature distinctly different selectivities. This E-nose can selectively detect breath relevant concentrations of acetone, ethanol and ammonia in 3analyte mixtures with estimation errors of only 38 ppb, 62 ppb and 111 ppb, respectively, outperforming clearly a *conventional* E-noses consisting of weakly selective doped SnO₂. This orthogonal E-nose shows the importance of sophisticated sensor selection for optimization of sensor arrays. It is promising for breath analysis to accurately sense multiple markers for noninvasive medical diagnostics (e.g. diabetes and kidney disease) and monitoring (e.g. hemodialysis).

A.1 Introduction

Electronic noses (E-noses) mimic the human olfactory system¹ with its high sensitivity and discrimination potential for odors.² The outstanding performance of the human nose is attributed to the combination of numerous differently sensitive receptors with their responses being processed in the olfactory cortex (Figure A.1a).² Similarly with E-noses, multiple differently selective sensors are combined that generate signals (e.g. resistance change for chemoresistive type)³ and subsequent statistical response analysis enables to differentiate odors (Figure A.1b).¹ In a recent study³, such an Enose (four differently doped SnO₂ sensors) had been applied to detect formaldehyde with low average estimation error (9 ppb) in 4-analyte mixtures at high relative humidity. However, it was also observed that the average estimation errors to ethanol (28 ppb), acetone (48 ppb) and ammonia (235 ppb) were significantly higher.³ This motivates further optimization of current E-noses to improve their estimation performance.

Different multivariate data analysis techniques had been applied to Enoses with the intention to increase the combinatorial selectivity of the rather non-specific constituent sensors.⁴ However, to reach the full potential of E-noses, engineering of the sensing materials needs to be pursued also to introduce stronger selectivity differences between the individual sensors.⁴⁻⁶ Ideally, such sensors combine to an array with *orthogonal* selectivity characteristics and this could enhance estimation stability and improve accuracy.⁶ The selectivity of chemoresistive gas materials is strongly affected by the material choice.⁷ While differently doped SnO₂ sensors show only weak selectivity to analytes, e.g. Si-doped α -MoO₃ to ammonia⁹, Sidoped ϵ -WO₃ to acetone¹⁰, or Ti-doped ZnO to isoprene.¹¹



Figure A.1: Comparison of human olfactory system (a) and E-nose (b). Olfactory system:³ Differently selective but non-specific receptors generate electrical signals upon analyte exposure. Signals are forwarded to the bulb and processed in the cortex for analyte classification. E-nose:² Differently selective but non-specific sensors are combined to an array and generate electrical signals upon analyte exposure. Subsequent statistical data analysis enables analyte identification in multicomponent gas mixtures.

Here, an *orthogonal* E-nose is presented that combines sensing materials with distinctly different selectivity. This array consists of three previously developed, flame-made, metal-oxide based gas sensors: Si-doped WO₃, Si-doped SnO₂ and Si-doped MoO₃. The potential for improved selective and simultaneous quantification of multiple analytes in 3-analyte mixtures (ammonia, acetone and ethanol) is investigated. Finally, its performance is compared to a *conventional* E-nose with weakly selective doped SnO₂ sensors.

A.2 Experimental

A.2.1 Particle and sensor fabrication

A flame spray pyrolysis reactor is used to produce sensing nanoparticles and directly depositing them onto sensor substrates.¹² A detailed description of the precursor solutions for Pd-doped SnO₂ (1 mol%),¹³ Si-doped SnO₂ (6 mol%),¹⁴ Pt-doped SnO₂ (0.15 mol%),¹⁵ Si-doped WO₃ (10 mol%))¹⁰ and Si-doped MoO₃ (3 wt%)⁹ can be found in the cited literature. The precursors are supplied at a feed rate of 5 mL min⁻¹ through a capillary and dispersed to fine droplets with 5 L min⁻¹ oxygen while keeping a pressure drop of 1.5 bar (1.6 bar for Si-doped MoO₃). The spray is ignited by a surrounding premixed methane/oxygen (1.25 L min⁻¹ / 3.2 L min⁻¹) flame. To ensure complete combustion additional sheath oxygen (5 L min⁻¹) is supplied through an annulus surrounding the flame.

Sensing films are produced by direct deposition of nanoparticles for 4 min through thermophoresis¹² onto $15 \times 13 \times 0.8$ mm Al₂O₃ substrates (Electronic Design Center, Case Western Reserve University). The substrate is mounted on a water-cooled holder and placed 20 cm above the burner. For the purpose of mechanical stability, adhesion and cohesion are increased by in situ annealing with a particle-free xylene flame for 30 s.¹⁶ The substrate holder is lowered to 14.5 cm above the burner and the same flame and sheath oxygen conditions are used as for deposition. Xylene is fed at 11 L min⁻¹ and dispersed with 5 L min⁻¹ oxygen. To avoid sintering and signal drift during testing, the sensors are thermally stabilized by annealing in an oven (Carbolite Gero 30-3000°C) for 10 h at 500 °C (doped SnO₂), 5h at 500 °C (Si-doped WO₃) or 5h at 450 °C (Si-doped MoO₃).

A.2.2 Sensor evaluation

The different sensing materials are assembled to a conventional (Pd-, Si- and Pt-doped SnO₂) and an orthogonal E-nose (Si-doped WO₃, Si-doped SnO₂ and Si-doped MoO₃). Each E-nose is tested separately in a Teflonmade three sensor chamber that is illustrated in Figure A.2a: The gas flow is directed through a diffuser followed by a sinter plate (gray) enabling homogenous distribution over all sensors. The sensors are attached to a Macor holder (blue) and connected to a power supply (R&S HMC8042, HAMEG) providing constant voltage to heat the sensors. Figure A.2b shows a cross-sectional view of that chamber: To minimize sensor interaction, the single sensors are positioned 14 mm apart and each sensing film is facing the heater of the neighboring sensor (separated by an angle of 120°). Doped SnO₂ (400 °C),³ Si-doped WO₃ (350 °C)¹⁷ and Si-doped MoO₃ (400 °C)⁹ are tested at their optimal operating temperature with respect to sensor performance as determined in the cited literature. Figure A.2c shows a schematic of the sensor substrates featuring a set of interdigitated Pt electrodes (sputtered, 350 µm width and spacing), a Pt resistance temperature detector (RTD) on the front and a Pt heater on the back side.

The sensor testing setup is described in detail elsewhere.⁹ The resistance of the sensing film between the interdigitated electrodes is measured by a Multimeter (2700, Keithley). Dry synthetic air (Pan Gas 5.0, C_nH_m and $NO_x \le 100$ ppb) is used as a carrier gas. Acetone (50 ppm in N₂, Pan Gas 5.0), ammonia (50 ppm in N₂, Pan Gas 5.0), ethanol (50 ppm in N₂, Pan Gas 5.0), NO (10 ppm in N₂, Pan Gas 5.0) and CO (500 ppm in N₂, Pan Gas 5.0) are controlled by calibrated mass flow controllers (Bronkhorst, Netherlands) and premixed with dry synthetic air to obtain the desired gas mixtures at a flow rate of 1 L min⁻¹.



Figure A.2: Schematic of the 3-sensor chamber in side (a) and cross-sectional (b) view with gas flow directed through a diffuser and a sinter plate (gray) to distribute the gas flow homogenously. The sensors (orange) are mounted on holders (blue). Dimensions are given in mm. (c) Nanoparticles (green) deposited on Al_2O_3 substrate with interdigitated Pt electrodes and a Pt resistance temperature detector on the front and a Pt heater on the back.¹⁷

A.2.3 Data Analysis

The sensor response S is calculated as follows⁹ with R_{air} representing the resistance obtained in dry synthetic air and $R_{analyte}$ the one when subjected to the analyte:

$$S = \frac{R_{air}}{R_{analyte}} - 1 \tag{1}$$

The sensitivity \sum is calculated in consistency with the technical standard DIN 1319-1:1995-01 5.4 by the following equation, where C represents the analyte concentration:

$$\Sigma = \frac{\partial S}{\partial C} \tag{2}$$

Breath relevant concentrations of ammonia (250, 500, 800, 1200, 1600 and 2000 ppb),¹⁸ acetone (250, 400, 600, 800, 1200 and 1800 ppb)¹⁹ and ethanol (50, 100, 150, 200, 400 and 600 ppb)¹⁹ are mixed to simulate breath. 60 (3-analyte mixture) randomly chosen combinations are tested.

A multivariate linear regression (MVLR) model is applied to estimate analyte concentrations in multicomponent gas mixtures. The applied model looks as follows:²⁰

$$\underline{C} = \underline{S} \cdot \underline{A} + \underline{U} \tag{3}$$

where <u>C</u> is the concentration matrix $(n \times p)$, with n samples and p analytes, <u>S</u> is the response matrix $(n \times m)$ for m sensors and <u>A</u> is the regressioncoefficients matrix $(m \times p)$ that first needs to be calibrated by ordinary least squares. <u>U</u> (normally distributed) is the residual error matrix.⁶ The average absolute estimation error ε_{avg} and the relative estimation error ε_{rel} are calculated as follows with n being the total number of measurement points:

$$\varepsilon_{avg} = \frac{\sum_{i=1}^{n} |c_{pred,i} - c_{act,i}|}{n} \tag{5}$$

$$\varepsilon_{rel} = \left| \frac{c_{pred,i}}{c_{act,i}} - 1 \right| * 100\% \tag{6}$$

Calculations are performed with MATLAB (version R2015b, MathWorks).

A.3 Results and discussion

A.3.1 Sensor selectivity and E-nose orthogonality

Figure A.3a shows the responses of Pd-, Si-, and Pt-doped SnO_2 sensors to breath realistic concentrations of ammonia (833 ppb, blue), acetone (477 ppb, green) and ethanol (112 ppb, purple) in dry air. These are normalized to the highest response for better comparability of the

selectivity. All sensors are only moderately specific with a highest response to acetone while it is weaker to ammonia and ethanol. The dopants alter the selectivity only little as observed already for similarly doped SnO₂ sensors³.

To investigate the collinearity of these sensors, their responses are illustrated as unit vectors in the 3-D analyte space with ammonia, acetone and ethanol representing the axis (Figure A.3b). The normalized response vectors of all three sensors are rather close, as expected from similar responses to the analytes (Figure A.3a), especially the ones of Pd- (orange) and Si-doped SnO₂ (red) that almost coincide. In fact, their vectors are only inclined by an angle of 2° while the one between Pt-doped (pink) and Si-doped SnO₂ is 11° and between Pt-doped and Pd-doped SnO₂ 10°.



Figure A.3: (a) Normalized responses of Pd-, Si- and Pt-doped SnO_2 to ammonia (833 ppb, blue), acetone (477 ppb, green) and ethanol (112 ppb, purple) tested in dry air. The responses for the individual sensors are normalized with respect to the highest ones. (b) The normalized responses of Pd- (orange), Si- (red) and Pt-doped (pink) SnO_2 are visualized as unit vectors in a 3-D analyte space.

This close alignment indicates a high degree of collinearity when combined to an array while being still linearly independent. This leads to instabilities in the matrix-inversion when estimating regression-coefficients



by MVLR, so small deviations in the monitored responses can result in large estimation errors.⁶

Figure A.4: (a) Normalized responses of Si-doped WO_3 , Si-doped SnO_2 and Sidoped MoO_3 to ammonia (833 ppb, blue), acetone (477 ppb, green) and ethanol (112 ppb, purple) in dry air. The responses for the individual sensors are normalized with respect to the highest value. (b) The normalized responses of Sidoped WO_3 (green), Si-doped SnO_2 (red) and Si-doped MoO_3 (blue) are visualized as unit vectors in a 3-D analyte space.

To increase *orthogonality*, enhanced selectivity variance of the array is necessary. This can be accomplished by the incorporation of highly and especially differently selective sensors, such as Si-doped WO_3^{10} and Sidoped MoO_3^{9} . The normalized responses of these sensors with an additional Si-doped SnO_2 one to concentrations of ammonia (833 ppb, blue), acetone (477 ppb, green) and ethanol (112 ppb, purple) are shown in Figure A.4a. Si-doped WO_3 exhibits the strongest response to acetone while Si-doped MoO_3 responds dominantly to ammonia, as expected from the literature^{9,10}. This is visible even better when converting the sensor responses again to unit vectors in the 3-D analyte space (Figure A.4b). Now, all vectors are separated clearly with an angle of 23° between Si-doped SnO₂ (red) and Sidoped WO₃ (green) while the latter is tilted more towards the acetone axis. In contrast, the Si-doped MoO₃ vector (blue) directs dominantly in direction of the ammonia axis. This results in an angle of 41° to Si-doped SnO₂ and 64° to Si-doped WO₃, respectively. As a results, incorporation of differently selective sensing materials increased the degree of orthogonality that should lead to a more accurate regression model and improved E-nose estimation of analytes in mixtures.⁶

A.3.2 E-nose performance in gas mixtures

The conventional and orthogonal E-noses are tested in 3-analyte mixtures containing 60 random combinations of breath relevant concentrations of ammonia (250 - 2000 ppb),¹⁸ acetone $(250 - 1800 \text{ ppb})^{19}$ and ethanol $(50 - 600 \text{ ppb})^{19}$ in dry air. Figure A.5 show the estimated acetone (a), ammonia (b) and ethanol concentrations (c) against their actual values in 3-analyte mixtures. The black circles represent the average estimation performance obtained by the conventional E-nose and the red triangles represent the ones obtained by the orthogonal E-nose. The dashed lines display ideal prediction and error bars indicate estimation variability for the corresponding concentrations.

Acetone is estimated by the *conventional* E-nose with an average error (ε_{avg}) of 131 ppb (Figure A.5d). This is improved significantly in case of the *orthogonal* E-nose by reducing ε_{avg} by more than 70% to only 38 ppb. So higher degree of orthogonality (Figure A.3b and A.4b) for an E-nose optimizes the estimation accuracy for acetone that has immediate impact on breath analysis. In fact, acetone is an important marker to detect diabetics²² and an accurate breath E-nose could facilitate easy diagnosis. An adequate quantification is also obtained for breath-relevant ammonia concentrations

by both E-noses (Figure A.5b). These concentrations are predicted with ε_{avg} of 116 ppb (conventional E-nose) and 111 ppb (orthogonal E-nose) (Figure A.5d). Interestingly, higher degree of orthogonality does not improve the estimation error ammonia and the reason for this needs to be investigated further. Nevertheless, the prediction accuracy of both arrays should be suitable to detect of end-stage renal disease in humans where concentrations are typically elevated by than several ppm compared to healthy states²³.



Figure A.5: Conventional (black circles) and orthogonal E-nose (red triangles) prediction of acetone (a), ammonia (b) and ethanol (c). Error bars indicate estimation variability for different interferent levels. 30 and 20 mixtures are used for MVLR calibration of the conventional and orthogonal E-nose, respectively. (d) The average prediction errors of the non-specific (black) and the orthogonal E-nose (red) for the individual analytes are plotted in this graph. A significant decrease of the prediction error for acetone and ethanol can be achieved by the orthogonal E-nose.

Finally for the ethanol prediction (Figure A.5c), the conventional Enose can hardly distinguish different concentrations leading to an ε_{avg} of 181 ppb (Figure A.5d). These large variations for the non-specific array might be caused by rather weak normalized ethanol responses and diminutive variance selectivity. This is changed drastically by the orthogonal E-nose. In fact, ε_{avg} is reduced by more than 65% to 62 ppb.

The accuracy enhancement observed for the acetone and ethanol prediction shows that higher degree of orthogonality significantly improves analyte concentration estimation in gas mixtures. This is similar to another studies where a conventional E-nose consisting of two SnO_2 sensors had been compared to a more orthogonal array consisting of a SnO_2 and a TiO_2 sensor.²⁴

A.4 Conclusions

This study demonstrates that estimation errors of current E-noses can be improved significantly by incorporation of sensors with distinctly different selectivity characteristics. Therefore, the performance of a *conventional* E-nose consisting of doped SnO₂ with rather collinear characteristics was compared to a more *orthogonal* E-nose (Si-doped MoO₃, Si-doped WO₃ and Si-doped SnO₂) with significant variance in selectivity between the sensors. By *orthogonalizing* the E-nose, the estimation errors to acetone and ethanol were reduced by more than 70% and 65%, respectively, compared to the *conventional* E-nose. As a result, this study highlights the importance to engineer novel materials with distinct and different selectivity properties. FSP is a great tool to seek for such sensing materials with unprecedented selectivity by exploring, for instance, novel and even metastable phases, solid solutions and mixed oxides with unique compositions.

A.5 References

- K. Persaud and G. Dodd, Analysis of discrimination mechanisms in the mammalian olfactory system using a model nose, *Nature*, 1982, 299, 352-355.
- [2] S. Firestein, How the olfactory system makes sense of scents, *Nature*, 2001, 413, 211-218.
- [3] A. T. Güntner, V. Koren, K. Chikkadi, M. Righettoni and S. E. Pratsinis, E-Nose Sensing of Low-ppb Formaldehyde in Gas Mixtures at High Relative Humidity for Breath Screening of Lung Cancer?, ACS Sens, 2016, 1, 528-535.
- [4] S. Marco and A. Gutierrez-Galvez, Signal and data processing for machine olfaction and chemical sensing: a review, *IEEE Sens. J.*, 2012, 12, 3189-3214.
- [5] J. Getino, M. Horrillo, J. Gutierrez, L. Ares, J. Robla, C. Garcia and I. Sayago, Analysis of VOCs with a tin oxide sensor array, Sens. Actuators B, 1997, 43, 200-205.
- [6] W. P. Carey, K. R. Beebe, E. Sanchez, P. Geladi and B. R. Kowalski, Chemometric analysis of multisensor arrays, *Sens. Actuators*, **1986**, 9, 223-234.
- [7] M. Righettoni, A. Amann and S. E. Pratsinis, Breath analysis by nanostructured metal oxides as chemo-resistive gas sensors, *Mater. Today*, 2015, 18, 163-171.
- [8] A. Galdikas, A. Mironas and A. Šetkus, Copper-doping level effect on sensitivity and selectivity of tin oxide thin-film gas sensor, *Sens. Actuators B*, 1995, 26, 29-32.
- [9] A. T. Güntner, M. Righettoni and S. E. Pratsinis, Selective sensing of NH₃ by Si-doped α-MoO₃ for breath analysis, *Sens. Actuators B*, 2016, 223, 266-273.

- [10] M. Righettoni, A. Tricoli and S. E. Pratsinis, Thermally stable, silicadoped ε-WO₃ for sensing of acetone in the human breath, *Chem. Mater.*, **2010**, 22, 3152-3157.
- [11] A. T. Güntner, N. J. Pineau, D. Chie, F. Krumeich and S. E. Pratsinis, Selective sensing of isoprene by Ti-doped ZnO for breath diagnostics, *J. Mater. Chem. B*, 2016, 4, 5358-5366.
- [12] L. M\u00e4dler, A. Roessler, S. E. Pratsinis, T. Sahm, A. Gurlo, N. Barsan and U. Weimar, Direct formation of highly porous gas-sensing films by in situ thermophoretic deposition of flame-made Pt/SnO₂ nanoparticles, *Sens. Actuators B*, **2006**, 114, 283-295.
- [13] J. Wang, P. Zhang, J.-Q. Qi and P.-J. Yao, Silicon-based micro-gas sensors for detecting formaldehyde, Sens. Actuators B, 2009, 136, 399-404.
- [14] A. Tricoli, M. Graf and S. E. Pratsinis, Optimal Doping for Enhanced SnO2 Sensitivity and Thermal Stability, *Adv. Funct. Mater.*, 2008, 18, 1969-1976.
- [15] L. M\u00e4dler, T. Sahm, A. Gurlo, J.-D. Grunwaldt, N. Barsan, U. Weimar and S. E. Pratsinis, Sensing low concentrations of CO using flamespray-made Pt/SnO2 nanoparticles, J. Nanopart. Res., 2006, 8, 783-796.
- [16] A. Tricoli, M. Graf, F. Mayer, S. Kuühne, A. Hierlemann and S. E. Pratsinis, Micropatterning Layers by Flame Aerosol Deposition-Annealing, *Adv. Mater.*, 2008, 20, 3005-3010.
- [17] M. Righettoni, A. Tricoli, S. Gass, A. Schmid, A. Amann and S. E. Pratsinis, Breath acetone monitoring by portable Si:WO₃ gas sensors, *Anal. Chim. Acta*, **2012**, 738, 69-75.
- [18] S. Davies, P. Spanel and D. Smith, Quantitative analysis of ammonia on the breath of patients in end-stage renal failure, *Kidney Int.*, 1997, 52, 223-228.

- [19] A. M. Diskin, P. Španěl and D. Smith, Time variation of ammonia, acetone, isoprene and ethanol in breath: a quantitative SIFT-MS study over 30 days, *Physiol. Meas.*, 2003, 24, 107.
- [20] K. V. Mardia, J. T. Kent and J. M. Bibby, *Multivariate analysis*, Academic press, London, 1979.
- [21] D. Smith, C. Turner and P. Španěl, Volatile metabolites in the exhaled breath of healthy volunteers: their levels and distributions, *J. Breath Res.*, 2007, 1, 014004.
- [22] C. Deng, J. Zhang, X. Yu, W. Zhang and X. Zhang, Determination of acetone in human breath by gas chromatography-mass spectrometry and solid-phase microextraction with on-fiber derivatization, J. *Chromatogr. B.*, 2004, 810, 269-275.
- [23] L. Narasimhan, W. Goodman and C. K. N. Patel, Correlation of breath ammonia with blood urea nitrogen and creatinine during hemodialysis, *P. Natl. A. Sci*, 2001, 98, 4617-4621.
- [24] B. Raman, D. C. Meier, J. K. Evju and S. Semancik, Designing and optimizing microsensor arrays for recognizing chemical hazards in complex environments, *Sens. Actuators B*, 2009, 137, 617-629.

Appendix B

Supplementary Data: E-nose sensing of low-ppb formaldehyde in gas mixtures at high relative humidity for breath screening of lung cancer?

Matlab Code for Multivariate Linear Regression

%The data set of measurement points is randomly divided into %a set of calibration and estimation points. %The set of calibration points is used in the following to %calculate %the MVLR coefficients. clear all, clc format, long %Sensor_responses for calibration: %Column 1:Pt:SnO2 response %Column 2:Si:SnO2 response %Column 3:Ti:SnO2 response %Column 4:Pd:SnO2 response %Xcalb(1,:) are the responses towards the gas mixture Y(1,:) Xcalb=[Manual Input]; %4-gas mixtures for calibration: %Column 1:Formaldehyde Concentration [ppb] %Column 2:Acetone Concentration [ppb] %Column 3:Ethanol Concentration [ppb] %Column 4:Ammonia Concentration [ppb] Ycalb=[Manual Input];

```
%Determination of the calibration coefficients
beta = mvregress(Xcalb,Ycalb);
8As
     а
         next
               step, analyte concentrations
                                                  are
estimated with the %set of sensor responses not used
for calibration % (independent).
%Xpred(i,:) contains the sensor responses of all
four sensors
Xpred = [Manual Input];
%Determine size of Xpred
[n,d] = size(Xpred);
%Define b to facilitate the code afterwards
b = [beta(1,1) beta(1,2) beta(1,3) beta(1,4)]
      beta(2,1) beta(2,2) beta(2,3) beta(2,4)
      beta(3,1) beta(3,2) beta(3,3) beta(3,4)
      beta(4,1) beta(4,2) beta(4,3) beta(4,4) ];
%estimation of the Formaldehyde concentration in the
gas %mixtures
for i=1:n
  Ypred(i,1)=Xpred(i,:)*b(:,1) + beta(5,1);
end
%Estimation of the Acetone concentration in the gas
mixtures
for i=1:n
   Ypred(i,2)=Xpred(i,:)*b(:,2) + beta(5,2);
end
%Estimation of the Ethanol concentration in the gas
mixtures
for i=1:n
   Ypred(i,3)=Xpred(i,:)*b(:,3) + beta(5,3);
end
```

```
%Estimation of the Ammonia concentration in the gas
mixtures
for i=1:n
    Ypred(i,4)=Xpred(i,:)*b(:,4) + beta(5,4);
end
```

Ypred;

```
%Finally, the estimated concentrations are compared
to the %actual ones %and the estimation error is
calculated.
%Actual Concentrations
Yact = [Manual Input];
%Calculate average estimation error for Formaldehyde
for i=1:n
    e(i,1) = abs(Ypred(i,1) - Yact(i,1));
end
%Calculate average estimation error for Acetone
for i=1:n
   e(i,2) = abs(Ypred(i,2) - Yact(i,2));
end
%Calculate average estimation error for Ethanol
for i=1:n
   e(i,3) = abs(Ypred(i,3) - Yact(i,3));
end
%Calculate average estimation error for Ammonia
for i=1:n
   e(i,4) = abs(Ypred(i,4) - Yact(i,4));
end
```
Appendix C

Supplementary Data:

Zeolite membranes for highly selective breath sensors

C.1 Sensor chamber design

Figure C.1 shows the chamber of the membrane-sensor device schematically. The zeolite MFI/Al_2O_3 membrane separates the sensing cavity from the outside. The membrane is fixed with a screw nut and additional O-rings for sealing to avoid any gas bypass.



Figure C.1: Dimensioned schematic of the sensor-membrane housing made out of stainless steel with a Pd-doped SnO_2 microsensor and zeolite/Al₂O₃ membrane (not true to scale).

C.2 Selectivity comparison

Figure C.2 shows the normalized responses of a Pd-doped SnO_2 sensor (400 °C) to breath-average concentrations of 60 ppb formaldehyde (blue), 600 ppb acetone (gray), 200 ppb ethanol (red) and 800 ppb NH₃ (green) for chamber A and B at 50% and 90% RH, respectively.



Figure C.2: Normalized responses of Pd-doped SnO_2 (400 °C) to breath-relevant 60 ppb formaldehyde (blue), 600 ppb acetone (gray), 200 ppb ethanol (red) and 800 ppb NH_3 (green) in chamber A (left) and B (right) at 50 and 90% RH, respectively. Data for chamber B are adapted from ¹. Normalization is done with respect to the maximum response for better selectivity comparison.

While in both cases, strongest responses are observed to acetone, the selectivities differ slightly. This could be associated to the different design of sensor chamber A (see Figure C.1) compared to B^1 . In case of chamber A, responses are probably diffusion-limited (compared to reaction-limited for B). As a result, molecules with higher diffusion coefficients result in relatively higher responses than these with lower ones and this can be observed on the example of NH₃ and acetone in Figure C.2. In case of

chamber A, the response to NH₃ compared to acetone is higher than in chamber B and this is in agreement to the higher diffusion coefficient of NH₃ compared to acetone with 0.218 and 0.103 cm² s⁻¹, respectively, as calculated with the Chapman-Enskog theory at standard conditions in air². Also different RH content (50% vs. 90%) can alter selectivity. In fact, higher RH increases the concentration of surface hydroxyl compared to oxygen-related species³ and this affects the reactivity of the sensing surface with each analyte individually.





Figure C.3: Responses of a Pd-doped SnO_2 sensor (with membrane) upon exposure to 10 ppm of TIPB (black), acetone (red), ethanol (blue) and methanol (light blue) at 50% RH. These response are significantly smaller than to 30 ppb of formaldehyde (green dashed line) highlighting the excellent selectivity of the membrane-sensor assembly.

C.4 References

- [1] A. T. Güntner, V. Koren, K. Chikkadi, M. Righettoni and S. E. Pratsinis, E-Nose Sensing of Low-ppb Formaldehyde in Gas Mixtures at High Relative Humidity for Breath Screening of Lung Cancer?, ACS Sens., 2016, 1, 528-535.
- [2] E. L. Cussler, *Diffusion: mass transfer in fluid systems*, Cambridge university press, 2009.
- [3] N. Barsan and U. Weimar, Understanding the fundamental principles of metal oxide based gas sensors; the example of CO sensing with SnO2 sensors in the presence of humidity, *J. Phys.-Condes. Matter*, 2003, 15, R813-R839.

Appendix C

Supplementary Data:

Body fat burn monitoring from exhaled acetone with Si-doped WO₃ sensing nanoparticles

D.1 Physiological data of subjects

Table D.1: Subject data

		_				
Subject	Gender	Age	Height	Weight	BMI	Additional
No.		(years)	(cm)	(kg)	(kg m ⁻²)	information
1	F	24	181	60	18.3	-
2	М	23	183	90	26.9	-
3	F	20	174	62	20.5	-
4	М	29	176	75	24.2	-
5	М	28	176	58	18.7	-
6	М	25	183	76	22.7	-
7	М	23	185	84	24.5	Asthma
						bronchiale,
						Atopie
8	F	27	160	53	20.7	-
9	F	33	170	80	27.7	Smoker
10	М	23	178	70	22.1	-
11	М	23	173	76	25.4	-
12	М	26	187	83	23.7	-
13	М	24	174	68	22.5	-
14	F	21	168	61	21.6	-
15	М	25	172	55	18.6	-
16	М	29	187	80	22.9	-
17	М	28	190	75	20.8	-
18	F	26	162	70	26.7	-
19	М	29	170	80	27.7	-
20	F	26	172	64	21.6	-



D.2 Breath acetone profiles of 20 volunteers

Figure D.1: Individual breath acetone data of 20 volunteers. (a-d) Breath acetone change (relative to initial value) measured by the sensor during testing with 3 x 30 min initial cycling and 3 h post-exercise rest (a, b) and as controls (c, d).



D.3 Breath acetone concentrations by PTR-TOF-MS

Figure D.2: Breath acetone concentrations during exercise and rest. Average breath acetone concentration measured by PTR-TOF-MS when tested with initial exercise (red triangles) and as control (blue squares). Note that bars indicate the standard deviation of 20 subjects and are shown only half-sided for better visibility.





Figure D.3: Agreement analysis between sensor and PTR-TOF-MS. Bland-Altman plot showing the differences between acetone change measured by sensor and PTR-TOF-MS as a function of the average values of both methods. Mean and mean $\pm 2\sigma$ of these differences are indicated as dashed and dash-dotted lines, respectively. The negligible mean difference (i.e. 0.0039) reveals no systematic bias³⁰ between the two methods and the limits of agreement (mean $\pm 2\sigma$: 0.288 and - 0.280) covering 95% of the differences are sufficiently low.

Curriculum Vitae

Andreas Güntner

July 23rd 1987, born in Albstadt-Ebingen, Germany, married, 1 child.

Education

2016	PhD in Mechanical Engineering, ETH Zurich, Switzerland.
2014	MSc with Distinction in Mechanical Engineering (GPA 5.85/6), ETH Zurich, Switzerland.
2012	BSc in Mechanical Engineering (GPA 5.34/6), ETH Zurich, Switzerland.
2007	Abitur, Gymnasium Hechingen (secondary school), Germany.

Professional Appointments

2017-	Co-founder and CEO of Sentiras GmbH, Zürich, Switzerland.		
2016-	Postdoctoral Fellow, Particle Technology Laboratory, ETH		
	Zürich, Switzerland.		
2014-2016	Graduate Research Assistant, Particle Technology Laboratory, ETH Zürich, Switzerland.		
2012-2013	Industrial Internship (6 months), MAN Diesel & Turbo AG, Zürich, Switzerland.		
2011	Undergraduate Research Assistant, Particle Technology Laboratory, ETH Zürich, Switzerland.		
2008	Industrial Internship (1 month), Grohman Aluworks, Bisingen, Germany.		
2007-2008	Civil Service, German Red Cross, Balingen, Germany.		
Awards			

2012	ETH Medal fo	r outstanding MSc	Thesis (top 2.5%).
------	--------------	-------------------	--------------------

Publications and Presentations

Refereed Journal Articles

- Blattmann C.O., Güntner A.T., Pratsinis S.E., "In situ monitoring the deposition of flame-made chemoresistive gas sensing films", ACS Appl. Mater. Interfaces, 9, 23926-23933, (2017).
- Güntner A.T., Pineau N.J., Chie D., Krumeich F., Pratsinis S.E., "Selective sensing of isoprene by Ti-doped ZnO for breath diagnostics", *J. Mater. Chem. B*, 4, 5358-5366, (2016). *Cover page*.
- Güntner A.T., Koren V., Chikkadi K., Righettoni M., Pratsinis S.E., "E-nose sensing of low-ppb formaldehyde in gas mixtures at high relative humidity for breath screening of lung cancer?", *ACS Sens.*, 1, 528-535, (2016).
- Güntner A.T., Righettoni M., Pratsinis S.E., "Selective sensing of NH₃ by Si-doped α-MoO₃ for breath analysis", *Sens. Actuators B*, 223, 266-273, (2016).
- Righettoni M., Ragnoni A., Güntner A.T., Loccioni C., Pratsinis S.E., Risby T.H., "Monitoring breath markers under controlled conditions", *J. Breath Res.*, 9, 047101, (2015).
- Oberbossel G., Güntner A.T., Kündig L., Roth C., Rudolf von Rohr P., "Polymer Powder Treatment in Atmospheric Plasma Circulating Fluidized Bed Reactor", *Plasma Process Polym.*, 12, 285-292, (2015).
- Waser O., Hess M., Güntner A., Novak P., Pratsinis S.E., "Size controlled CuO nanoparticles for Li-ion batteries", *J. Power Sources*, 241, 415-422, (2013).
- Güntner A.T., Abegg S., Wegner K., Pratsinis S.E., "Zeolite membranes for highly selective breath sensors", *submitted*.
- Güntner A.T., Sievi N.A., Theodore S.J., Gulich T., Kohler M., Pratsinis S.E., "Body fat burn monitoring from exhaled acetone with Si-doped WO₃ sensing nanoparticles", *submitted*.

- Güntner A.T., Pineau N.J., Mochalski P., Agapiou A., Pratsinis S.E., "Electronic nose monitoring of breath and skin-emitted tracers of entrapped humans", *submitted*.
- Mochalski P., Ruzsanyi V., Wiesenhofer H., Allers M., Zimmermann S., Güntner A.T., Pineau N.J., Agapiou A., Mayhew C.A., "Monitoring selected skin- and breath-borne volatile organic compounds emitted from the human body using gas chromatography ion mobility spectrometry (GC-IMS)", *submitted*.
- Güntner A.T., Schon S., Theodore S.J., Sievi N.A., Kohler M., Pratsinis S.E., "Simple and versatile breath sampler design for online gas sensor analysis", *in preparation*.
- Güntner A.T., Pineau N.J., Pratsinis S.E., "Electronic nose 2.0: towards *orthogonal* sensor arrays by selective material design", *in preparation*.
- Güntner A.T., Pratsinis S.E., "Designing selective gas sensors for single breath marker monitoring: How to?", *in preparation*.

Patent Applications

- "Breath analyser", Güntner A.T., Pratsinis S.E., CH 1567/16, November 2016.
- "Device and method for detecting gas", Güntner A.T., Abegg S., Wegner K., Pratsinis S.E., *CH 1459/16, November 2016.*

Press Releases

- 2017 Deutschlandfunk radio interview (in German) on breath analysis for disease detection: http://www.deutschlandfunk.de/tolle-idee-was-wurde-daraus-atemtest-fuer-diabetiker.676.de.html?dram:article_id=389137
- 2017 Hochschulmedizin Zürich article (in German) on small nanostructured breath sensors: http://www.hochschulmedizin.uzh.ch/de/newsletterarchiv.html
- 2017 SRF Puls TV show (in German) on breath sensors for lung cancer detection: http://www.srf.ch/sendungen/puls/fuer-diagnose-bitte-blasen

Presentations

Talks and seminars

- "Lung cancer detection from breath? Portable E-nose for selective low-ppb formaldehyde sensing", *MRS Fall Meeting;* Boston, USA (27/11-2/12/2016). *upcoming*
- 9. "E-nose for selective formaldehyde detection in breath analysis", *IABR Summit;* Zürich, Switzerland (14-16/9/2016).
- 8. "Lung cancer detection from breath? Portable E-nose for selective low-ppb formaldehyde sensing", **invited** seminar at the *Department of Chemical Engineering* at the *Hiroshima University*; Hiroshima, Japan (28/7/2016).
- 7. "Analyte-selective MOx sensor systems from flame aerosols for breath analysis", **invited** seminar at the *Electroceramics Research Group* of the *National Institute of Advanced Industrial Science and Technology*; Nagoya, Japan (15/7/2016).
- 6. "Lung cancer detection from breath? Portable E-nose for selective low-ppb formaldehyde sensing", **invited** seminar at the *Department of Complex Systems Science* at the *University Nagoya*; Nagoya, Japan (15/7/2016).
- 5. "Selective isoprene sensing for breath analysis by Ti-doped ZnO chemoresistive sensors", *IMCS Meeting*; Jeju Island, Korea (10-13/7/2016).
- 4. "Cancer detection from breath? Aldehyde sensing by nanostructured microsensor arrays", *Partec Conference;* Nuremberg, Germany (19-21/4/2016).
- 3. "Portable breath analyzers: Selective analyte detection by tailored and nanostructured metal-oxides", **invited** seminar at the *Department of Chemistry* at the *University of Cyprus*; Nicosia, Cyprus (19/10/2015).
- 2. "Towards portable breath analyzers: Selective analyte detection by tailored and nanostructured metal-oxides", **invited** seminar at the *Micro- and Nanosystems Group* at the *ETH Zürich*; Zürich, Switzerland (2/10/2015).
- 1. "Selective NH₃ detection by portable Si-doped α-MoO₃ sensor for breath analysis", *IABR Summit;* Vienna, Austria (14-16/9/2015).

Posters

- 22. "Fat burn monitoring during exercise with flame-made Si:WO₃ breath sensors", *MRS Fall Meeting;* Boston, USA (27/11-2/12/2016). *upcoming*
- 21. "Carcinogenic isoprene detection at low-ppb level with nanostructured Tidoped ZnO sensors", *MRS Fall Meeting;* Boston, USA (27/11-2/12/2016). *upcoming*
- 20. "Morphology-controlled flame patterning of thermally sensitive films on Si wafers", *MRS Fall Meeting;* Boston, USA (27/11-2/12/2016). *upcoming*
- 19. "Selective isoprene detection by portable Ti-doped ZnO sensors", *IABR Summit;* Zürich, Switzerland (14-16/9/2016).
- "Miniaturizing sensors for portable breath analyzers", *IABR Summit;* Zürich, Switzerland (14-16/9/2016).
- 17. "Analyte selective sensor materials by flame aerosol synthesis", *IABR Summit;* Zürich, Switzerland (14-16/9/2016).
- 16. "Novel nano-structured materials from flames: towards analyte-selective sensing", *IMCS Meeting;* Jeju Island, Korea (10-13/07/2016).
- 15. "Lung cancer detection from breath ? Portable E-nose for selective low-ppb formaldehyde sensing", *IMCS Meeting*; Jeju Island, Korea (10-13/07/2016).
- "Kidney disease detection and monitoring by breath analysis: selective sensing of NH₃ by Si-doped α-MoO₃", *IMCS Meeting*; Jeju Island, Korea (10-13/07/2016).
- "Kidney disease detection and monitoring by breath analysis: selective sensing of NH₃ by Si-doped α-MoO₃", *MaP Graduate Symposium*; Zürich, Switzerland (9/06/2016).
- 12. "Cancer detection from breath? Portable E-nose for selective low-ppb formaldehyde sensing", *MaP Graduate Symposium;* Zürich, Switzerland (9/06/2016).
- "Kidney disease detection & monitoring via breath ammonia sensing by tailored Si-doped MoO₃", *Partec Conference;* Nuremberg, Germany (19-21/04/2016).
- 10. "Flame-made ZnO for enhanced acetone sensing in breath analysis", *Partec Conference;* Nuremberg, Germany (19-21/04/2016).

- 9. "Cancer detection from breath? Aldehyde sensing by nanostructured microsensor arrays", *Partec Conference;* Nuremberg, Germany (19-21/04/2016).
- "Cancer Detection from breath? aldehyde sensing by microsensor arrays", MRS Fall Meeting; Boston, USA (29/11-4/12/2015), Best Poster Award nominee.
- "Si-Doped MoO₃: from nanobelts to –needles improving breath NH₃ sensing for end-stage renal disease monitoring", *MRS Fall Meeting*; Boston, USA (29/11-4/12/2015).
- 6. "Room temperature gas sensor based ε-WO₃-polyaniline nanocomposite ", *MRS Fall Meeting;* Boston, USA (29/11-4/12/2015).
- 5. "Flame-made ZnO for Enhanced Acetone Sensing in Breath Analysis", *MRS Fall Meeting;* Boston, USA (29/11-4/12/2015).
- 4. "Towards portable breath analyzers for disease detection and monitoring: NH₃, acetone, ethanol and formaldehyde sensing by nanostructured MOx arrays", *MRS Fall Meeting;* Boston, USA (29/11-4/12/2015).
- 3. "Highly crystalline Si-doped α-MoO₃ for NH₃ detection at the ppb-level", *IABR Summit;* Vienna, Austria (14-16/09/2015).
- "Ammonia detection by MoO₃-based gas sensor for breath analysis ", *MRS Fall Meeting;* Boston, USA (30/11-5/12/2014).
- "Size controlled flame synthesis of copper oxide nanoparticles for Li-ion conversion reaction electrodes", *MRS Fall Meeting;* Boston, USA (28/11-2/12/2011).

Services

Scientific Leadership

- 2016 Session Chair, *MRS Fall Meeting*, Boston, USA.
- 2016 Scientific Committee, *IABR Summit*, Zürich, Switzerland.
- 2015 Session Chair, *IABR Summit*, Vienna, Austria.

Reviewing for Scientific Journals

ACS Applied Materials & Interfaces Analytical Chemistry Electrophoresis Industrial & Engineering Chemistry Research Journal of Breath Research Langmuir Nanoscale Progress in Energy and Combustion Science Scientific Reports Sensors Sensors Sensors and Actuators B: Chemical Surfaces and Interfaces