Towards the Single Breath Disease-Diagnosis Breathalyzer

Perena Gouma

https://web.stonybrook.edu/cnsd/formservertemplates/page.html

OUR PORTABLE, HANDHELD, POINT OF CARE BREATHALYZER

http://www.nsf.gov/news/special_reports/science_nation/breathprinting.jsp

EVERYONE CAN PROVIDE A SINGLE BREATH (EXHALE) SAMPLE

http://www.pipa.org.au/

http://www.attorneyhoyle.com/aging_incapacity.html

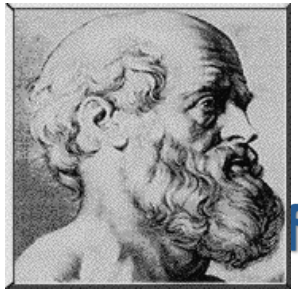
http://www.armytimes.com/article/20130128/NEWS/301280315/Fleetwide-breath-tests-start-now

http://flickrhivemind.net/

Point-of-Care Breath Diagnostics

BREATH GASES AS DISEASE MARKERS

TIMELINE OF BREATH ANALYSIS



Antiquity: Hippocrates fetor hepaticus

Linus Pauling's GC analysis of breath

The Dawn of Nanomedicine

Hippocrates of Cos (ca. 460 BC – ca. 370 BC) – father of modern medicine

1972
Orthomolecular medicine

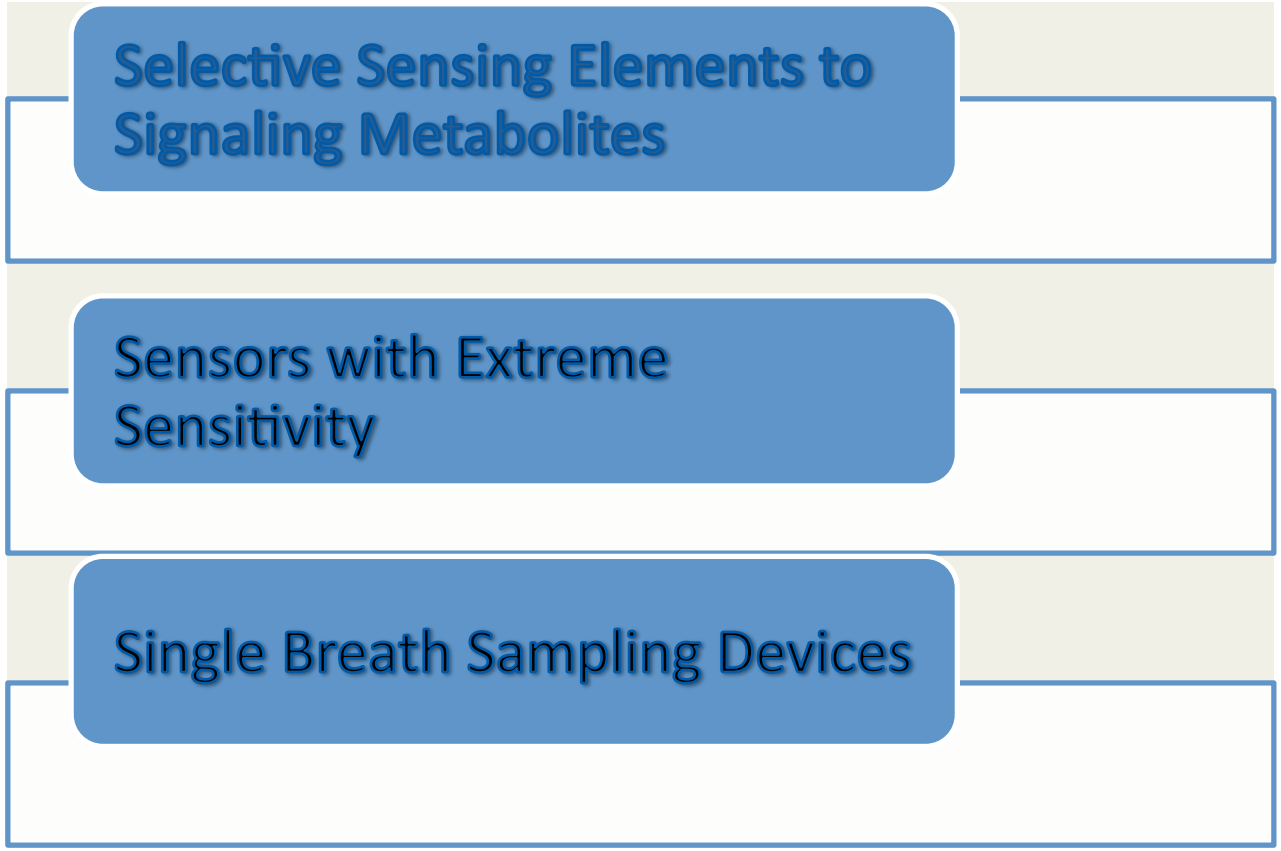
2000
Nanotechnology for prevention, early detection and treatment of disease

Breath Analysis

CAPTURE YOUR BREATH

- **Over 1000 compounds**
- **Trace Concentrations**
- **Sampling Issues**

THE CHALLENGE TO DEVELOP A PORTABLE, SIMPLE, BREATHALYZER



NEED FOR "EXTREME" SENSOR SENSITIVITY

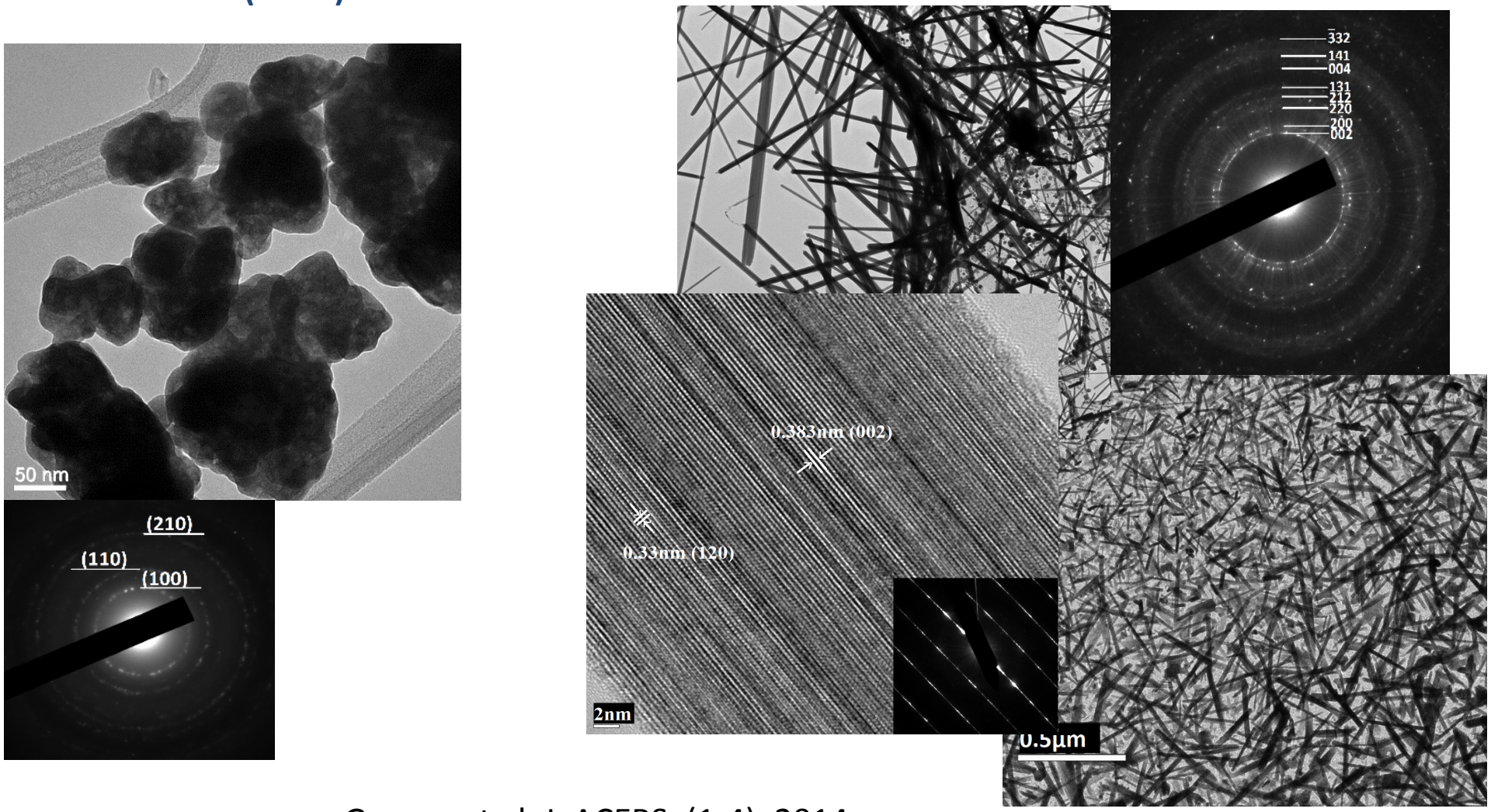
Biomarkers	Physiological origin	Related diseases	Physiological ranges in human breath
Ethane	Lipid peroxidation	Oxidative stress	1-11 ppb
Pentane	Lipid peroxidation	Oxidative stress	Less than ethane
Isoprene	Cholesterol biosynthesis	Cholesterol metabolic disorder	55-121 ppb; 12-580 ppb;
Acetone	Decarboxylation of acetoacetate and acetyl-CoA	Diabetes mellitus, ketonemia	293-870 ppb; 1.2-1880 ppb
Ethanol	Alcohol ingestion	Alcohol poisoning	27-153 ppb; 13-1000 ppb
Methanol	Degradation of natural pectin from plants; ingestion	Methanol intoxication	160-2000 ppb
NH_3	Metabolic product of amino acid deamination	Uremia, kidney impairment	422-2389 ppb; 200-1750 ppb
CO	Inhalation from In-complete burning of carbon containing fuels, e.g. smoking	Lung diseases	<6 ppm
NO	L-arginine oxidation	Asthma, lung diseases	1-9 ppb, lower respiratory; 0.2-1 ppm upper respiratory; 1-30 ppm, nasal level.

A. Amann and D. Smith, *Breath Analysis for Clinical Diagnosis and Therapeutic Monitoring,* World Scientific, Singapore, 2005

High-Energy Electron Beam Lithography

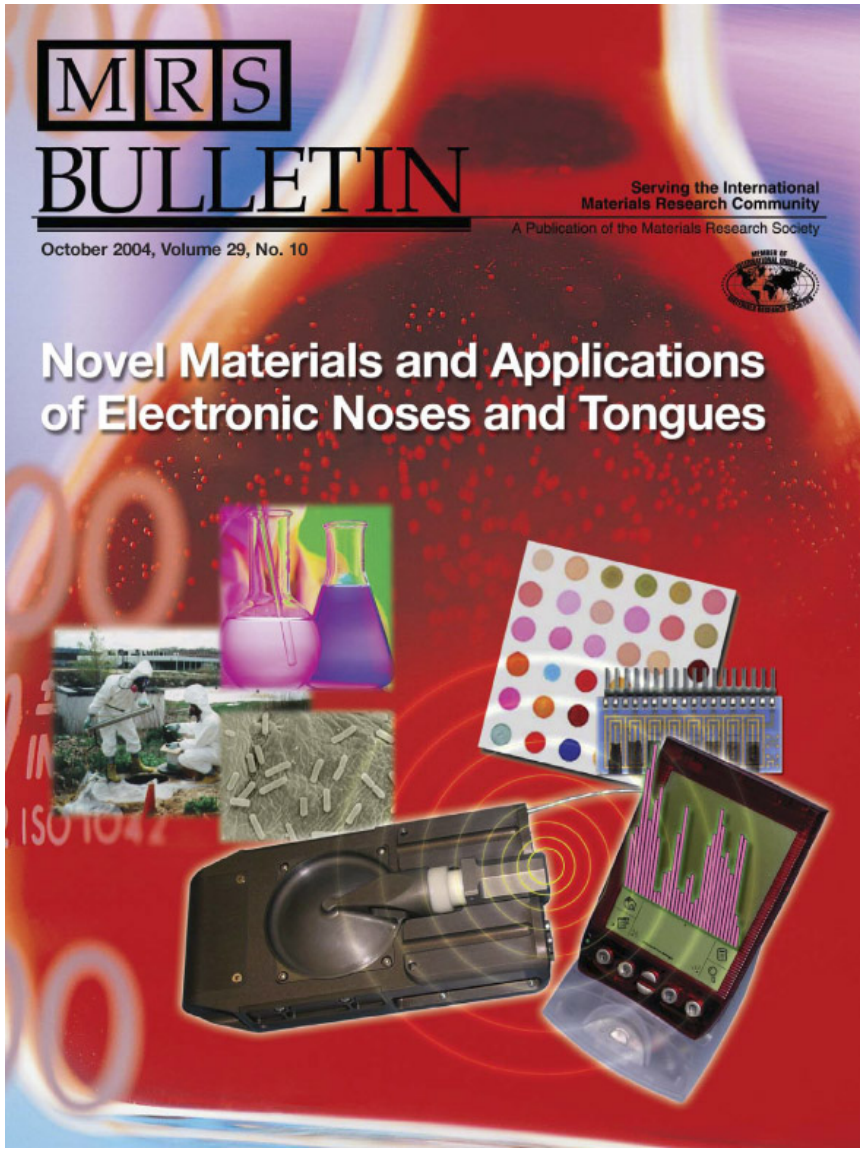
based on polymorphic phase reactions

Metastable (cubic) ⟷ **Stable (monoclinic)**



Gouma et al, J. ACERS, (1-4), 2014

THE NON-SELECTIVE SENSOR-ARRAY ELECTRONIC OLFACTION CONCEPT



P. Gouma and G. Sberveglieri, “Novel Materials and Applications of Electronic Noses and Tongues”, MRS Bulletin, 29 (10), pp. 697-700, 2004.

OUR GAS-SELECTIVE BREATHALYZER

http://www.nsf.gov/news/special_reports/science_nation/breathprinting.jsp

Transformative Technology:

- Inexpensive, affordable, non-invasive, health-promoting tool

- Novel portable device with capability of transmitting data wirelessly to health care providers

- Permits prompt decision making by professionals remotely without necessitating a trip to a hospital or health care facility

Beyond BAC: How the Breathalyzer Is Poised to Revolutionize Medical Diagnostics

http://mashable.com/2011/09/07/breathalyzer-medicine/

“Dr. Gouma's team's nanosensors utilize resistive semiconducting technology — they make for a scientific yet economic tool (roughly $20 per breathalyzer) that allow her to test for particular chemicals.”

CRYSTALLO-CHEMICAL APPROACH TO SELECTIVE CHEMOSENSING

Group A: oxides having the ReO_3 structure

(γ-WO_3, β-MoO_3)

NO

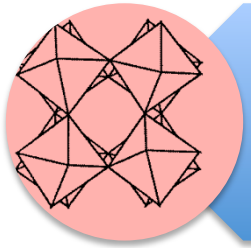
marker for inflammation in lungs

Group B: oxides having a weakly bonded layered structure

(α-MoO_3, h-WO_3)

Ammonia

marker for renal diseases

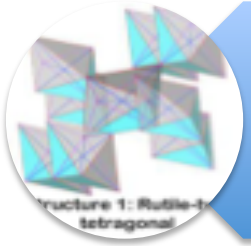


Group C: acentric crystal structures-ferroelectric polymorphs

(ε-WO_3)

Acetone

correlates with insulin levels in the body



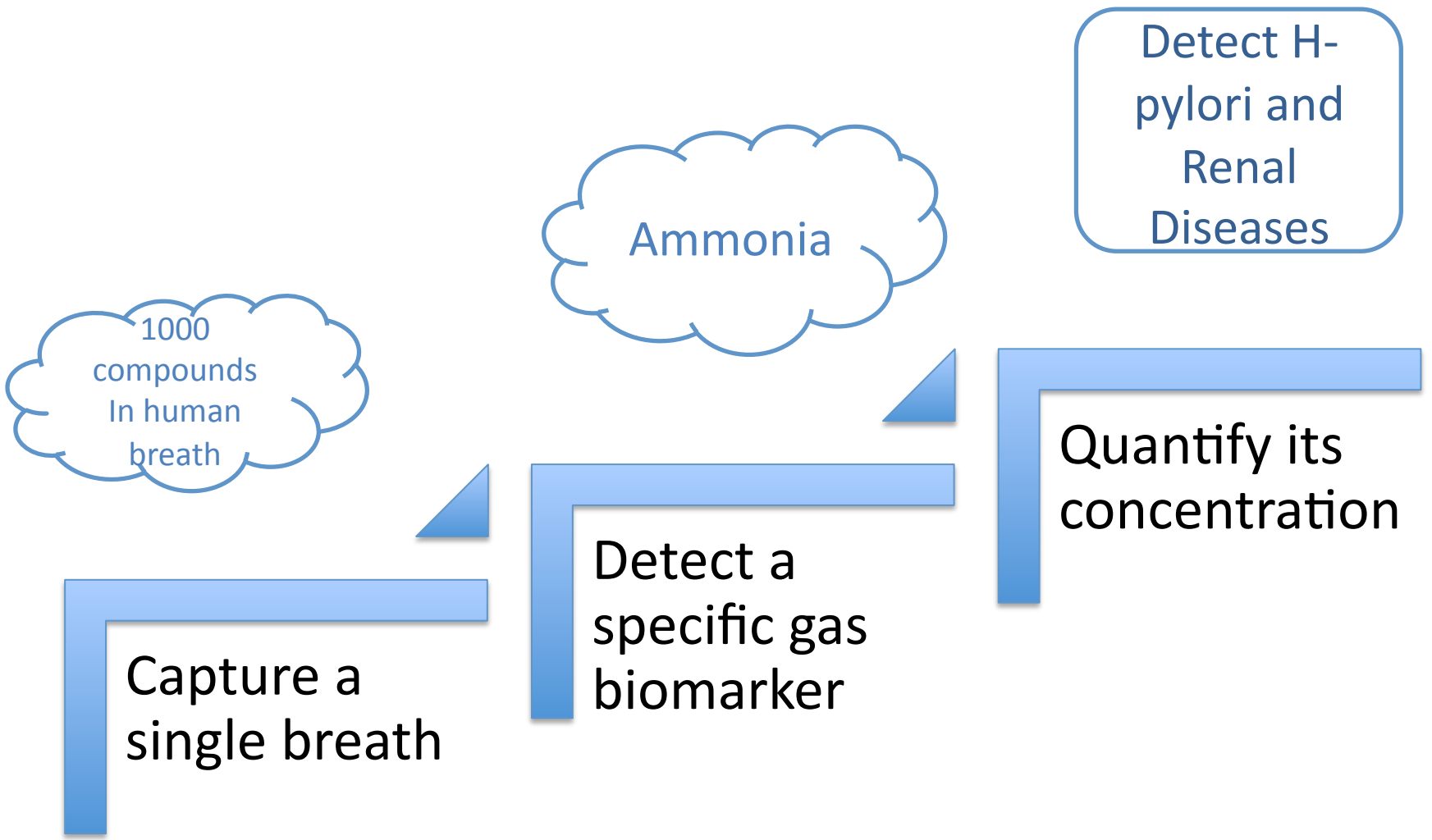
Group D: oxides having the rutile structure

(TiO_2, SnO_2, IrO_2, MnO_2)

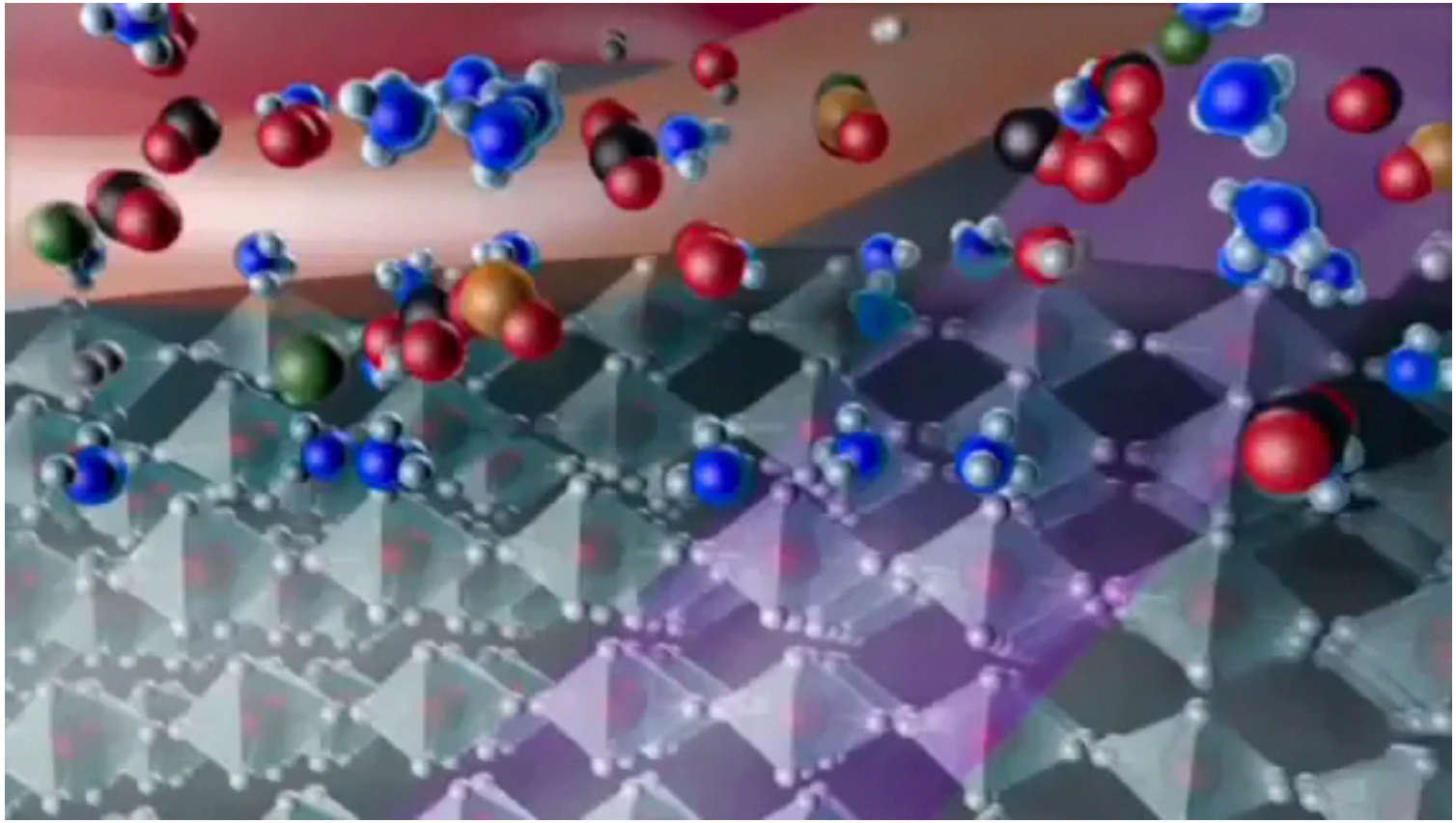
CO

marker for cardiovascular diseases

P. Gouma,*Science of Advanced Materials*, 3(5), pp. 787-793, 2011.


Detect H-pylori and Renal Diseases
Ammonia
1000 compounds In human breath
Quantify its concentration
Detect a specific gas biomarker
Capture a single breath

α-MoO_3 NANOWIRES SHOW SPECIFICITY TO AMMONIA GAS DETECTION



http://www.nsf.gov/news/special_reports/science_nation/breathprinting.jsp

US007017389B2

(12) **United States Patent**
Gouma

(10) **Patent No.: US 7,017,389 B2**
(45) **Date of Patent: Mar. 28, 2006**

(54) **SENSORS INCLUDING METAL OXIDES SELECTIVE FOR SPECIFIC GASES AND METHODS FOR PREPARING SAME**

(75) Inventor: **Pelagia-Irene Gouma**, Port Jefferson, NY (US)

(73) Assignee: **The Research Foundation of SUNY at Stony Brook**, Stony Brook, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/419,349**

(22) Filed: **Apr. 21, 2003**

5,858,186	A	1/1999	Glass	
5,969,231	A *	10/1999	Qu et al.	73/31.05
5,993,625	A *	11/1999	Inoue et al.	204/425
6,173,602	B1	1/2001	Moseley	

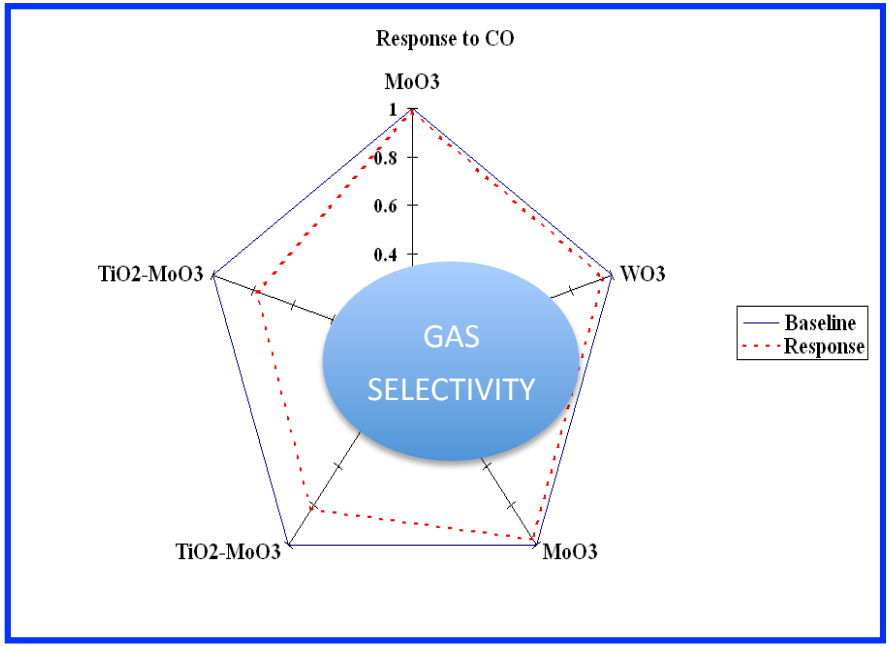
OTHER PUBLICATIONS

Imawan et al., "Gas-sensing characteristics of modified-MoO_2 thin films using Ti-overlayers for NH_3 gas sensors", *Sensors and Actuators* B 64 (2000) pp. 193-197.

Imawan et al., "A new preparation method for sputtered MoO_3 multilayers for the application in gas layers", *Sensors and Actuators* B 78 (2001) pp. 119-125.

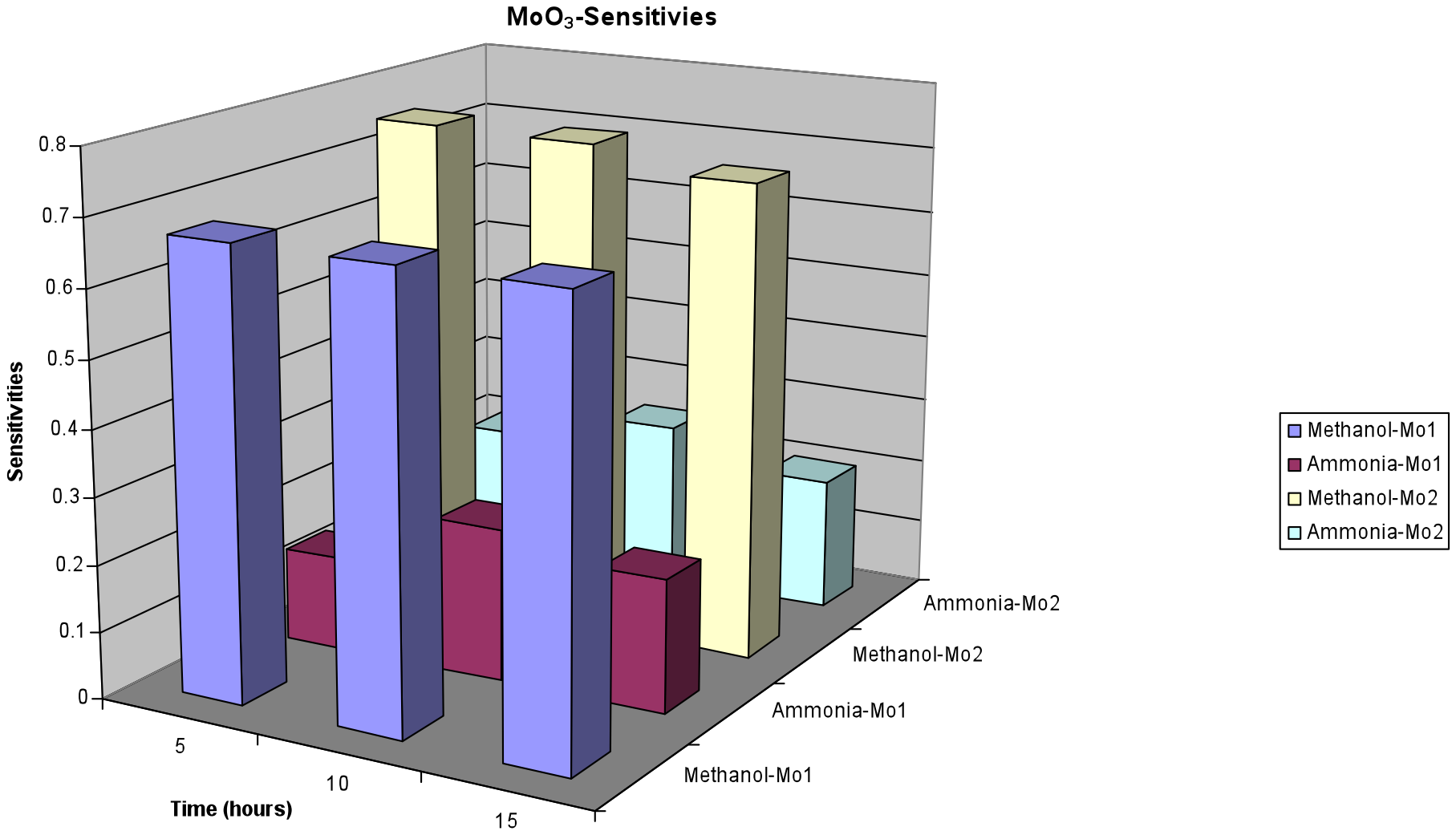
Ferroni et al., "Nanosized thin films of tungsten-titanium mixed oxides as gas sensors", *Sensors and Actuators* B 58 (1999) pp. 289-294.

Chung et al., "Gas sensing properties of WO_3 thick film for NO_2 gas dependent on process condition", *Sensors and Actuators* B 60 (1999) pp. 49-56



P.I. Gouma, A. K. Prasad, and K.K. Iyer, "Selective Nanoprobes for `Signaling Gases`", *Nanotechnology*, 17, pp. S48-S53, 2006.

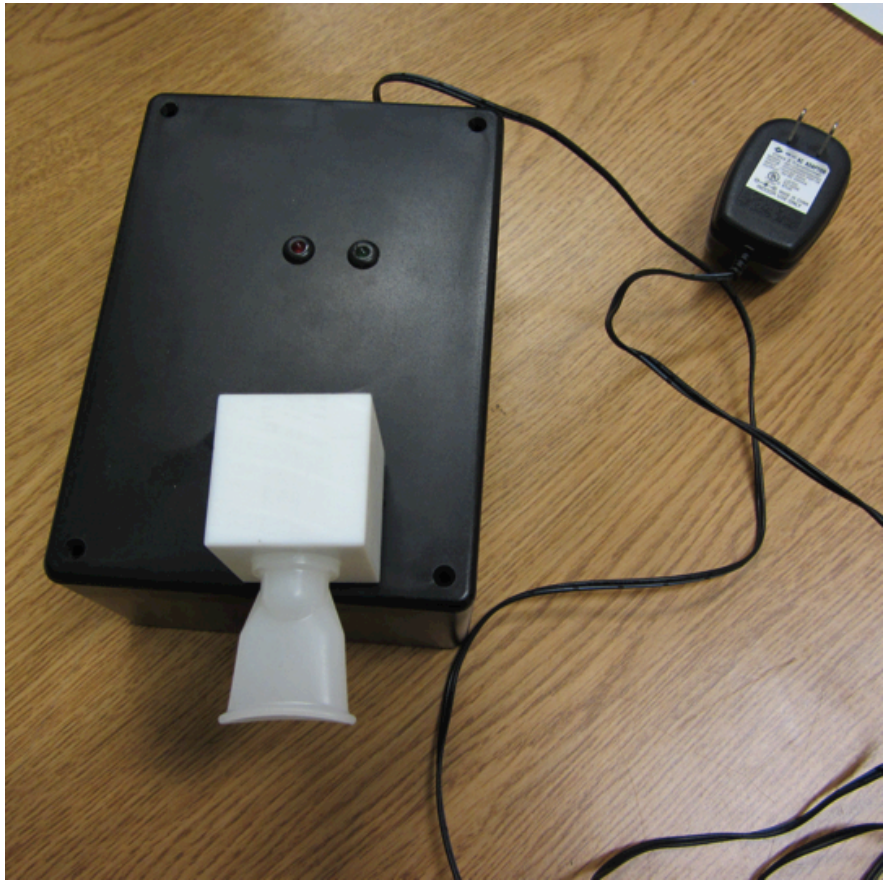
SELECTIVE GAS SENSOR ARRAYS



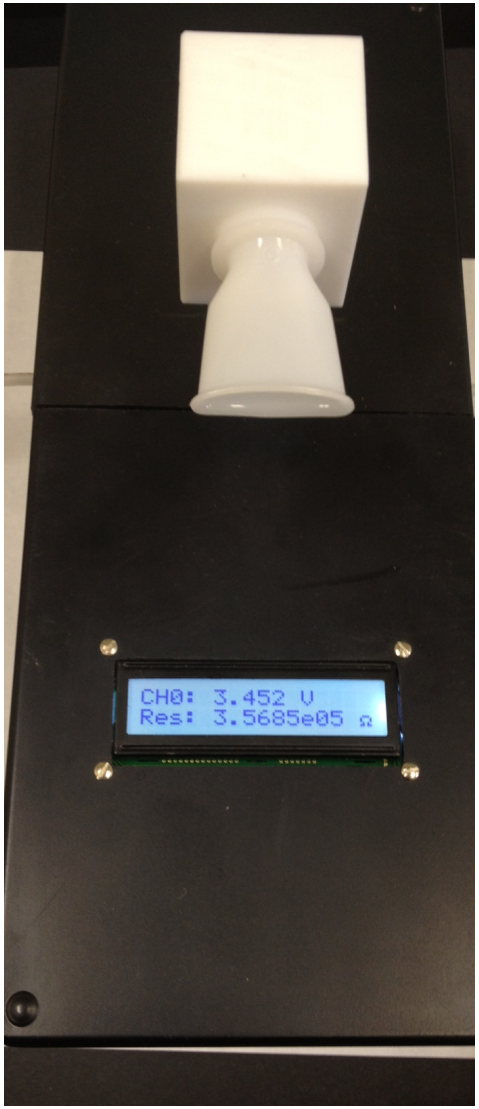
P. Gouma, "Nanostructured Oxide-based Selective Gas sensor Arrays for Chemical Monitoring and Medical Diagnostics in Isolated Environments", *Habitation Journal*, vol. 10 (2), pp. 99-104, 2005.

BREATHALYZER PROTOTYPES

BINARY, ON-OFF MODEL



NUMERICAL



INTERFACING WITH MOBILE DEVICES

http://www.insidescience.org/content/cellphones-detecting-asthma/980

P. Gouma, “Nanoceramic Sensors for Medical Applications”, Am. Ceram. Soc. Bulletin, 91 (7), pp. 26-31, September 2012.

Portable, Affordable, Non-invasive, Asthma Monitoring

Application:

- **Nitric Oxide (NO) breathalyzer for monitoring of airway diseases** (such as asthma)
- consumer product, personalized monitoring of **fractional nitric oxide concentration (FENO)** in breath, home use
- Competition: three FDA approved devices for hospital use only costing $$$s

Biomarkers:

- Key biomarker: **NO** in breath
- Measuring FENO measures airway inflammation
- NO is detectable in exhaled air in significant amounts: from 0.2–1 ppm in the upper respiratory tract; and 1–30 ppm at the nasal level
- Both the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have published guidelines for the measurement of FENO:

Dweik et al, "Am. J. Respir. Crit. Care Med, 184, pp. 602, 2011

Validation:

- Sensor tests measuring NO concentrations ranging from 100ppb to several ppm have been carried out using synthetic air mixtures
- Prototyping of portable breathalyzer

P.I Gouma et al, "A Selective Nanosensing Probe for Nitric Oxide", Applied Physics Letters, 93, 2008.

Application #1: Metabolic Rate Monitor

Application:

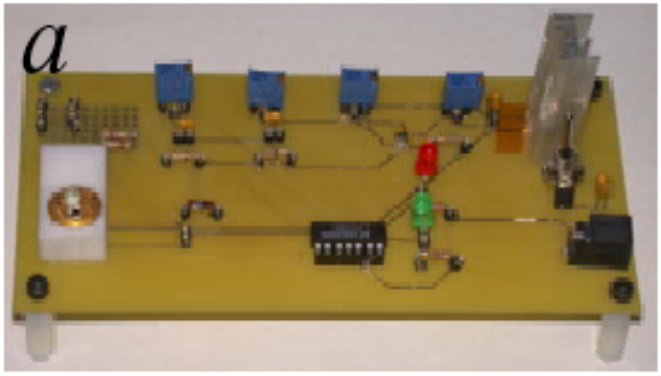
- **Handheld breath-acetone monitor for diet control**
- Consumer product for diet control, daily repeated use, gives consumer direct measure of fat metabolism, indicates whether fat is burned instead of muscle

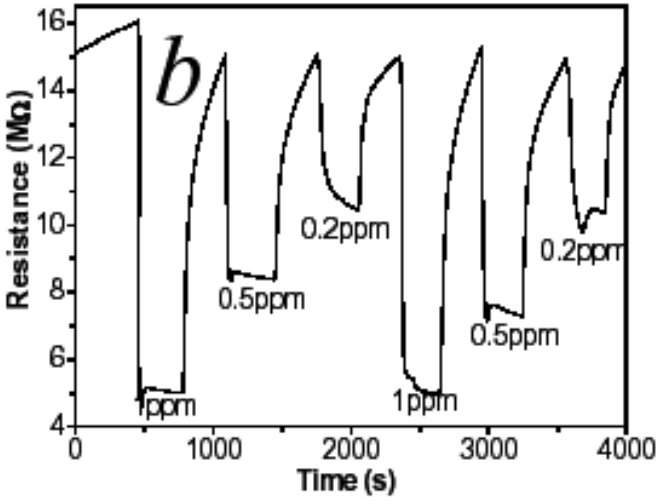
Biomarkers:

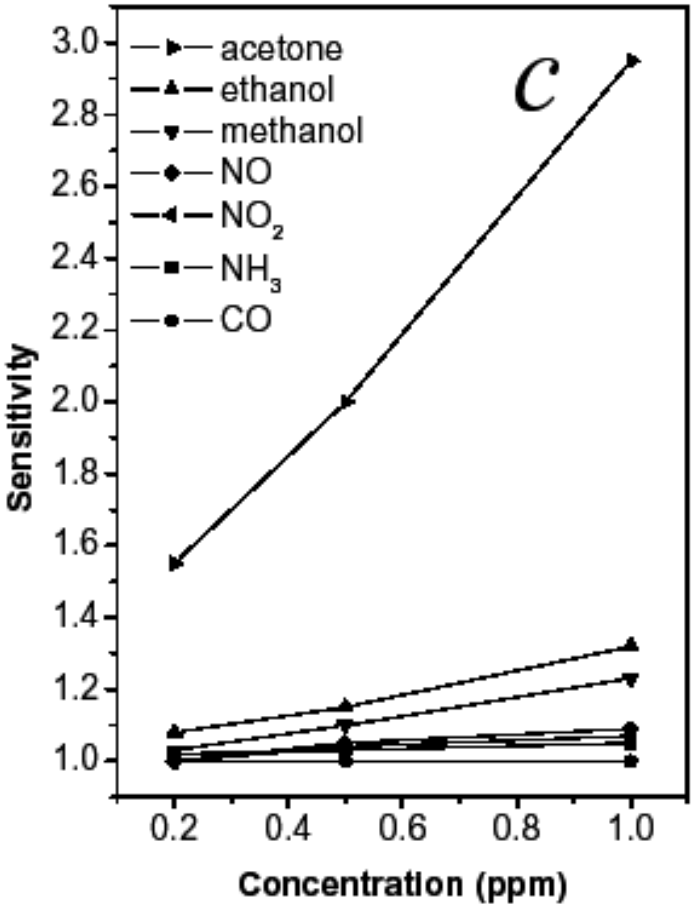
- key biomarker**: acetone in breath**
- lipid degradation product
- Breath acetone of 500nmol/L indicates a weight reduction of about one-half pound per week ***http://www.clinchem.org/content/29/1/5.full.pdf***
  - The minimum acetone concentration that needs to be detected is 200ppb
  - Acetone content increases fivefold by day 3-4 so the maximum concentration to be detected should be few ppm

P. Gouma et al, "Metabolic Rate Monitoring and weight reduction/management", EMBC, 2014
P. Gouma, Person. Med. , 8(1), pp. 15-16, 2011

Acetone Breathalyzer for Diet Control







Gouma's group: **Nanosensor Device for Breath Acetone Detection"**
Sensor Lett., 8(1-4), 2010

Application #2: Diabetes Monitoring

Application:

- **Hand-held breath acetone monitor for insulin levels control in diabetics**
- consumer product for daily use

Biomarkers:

- Key biomarker: **acetone** in breath
- Acetone in breath is a more sensitive indicator of poor control of diabetes than blood glucose ***Barnett, Clin Sci. 37, 570, 1969***
- Average concentration of acetone in the breath from a healthy human body <800ppb (0.8ppm) while that from a diabetic patient is >1.8ppm
-
- For individuals suffering from diabetic ketoacidosis, the acetone concentration can exceed 500ppm

L. Wang and P. Gouma, "Selective Microstructure Synthesis and Sensing Dependencies: a WO_3 study", in Metal Oxide Nanomaterials for Chemical Sensors, eds. M. A. Carpenter, Sanjay Mathur, and Andrei Kolmakov, Springer, NY, 2013.

Acetone Breathalyzer for Diabetes Monitoring

Approximately linear relationship between Acetone Concentration and Sensor Sensitivity:

$$S = 1.19 + 1.68C$$

Empirical formula calculating the Acetone concentration between 0.2 ppm and 2 ppm

From L. Wang (Gouma's advisee), Ph.D. thesis, **"Tailored Synthesis and Characterization of Selective Metabolite-detecting Nanoprobes for Handheld Breath Analysis"** ***SUNY Stony Brook, 2008***

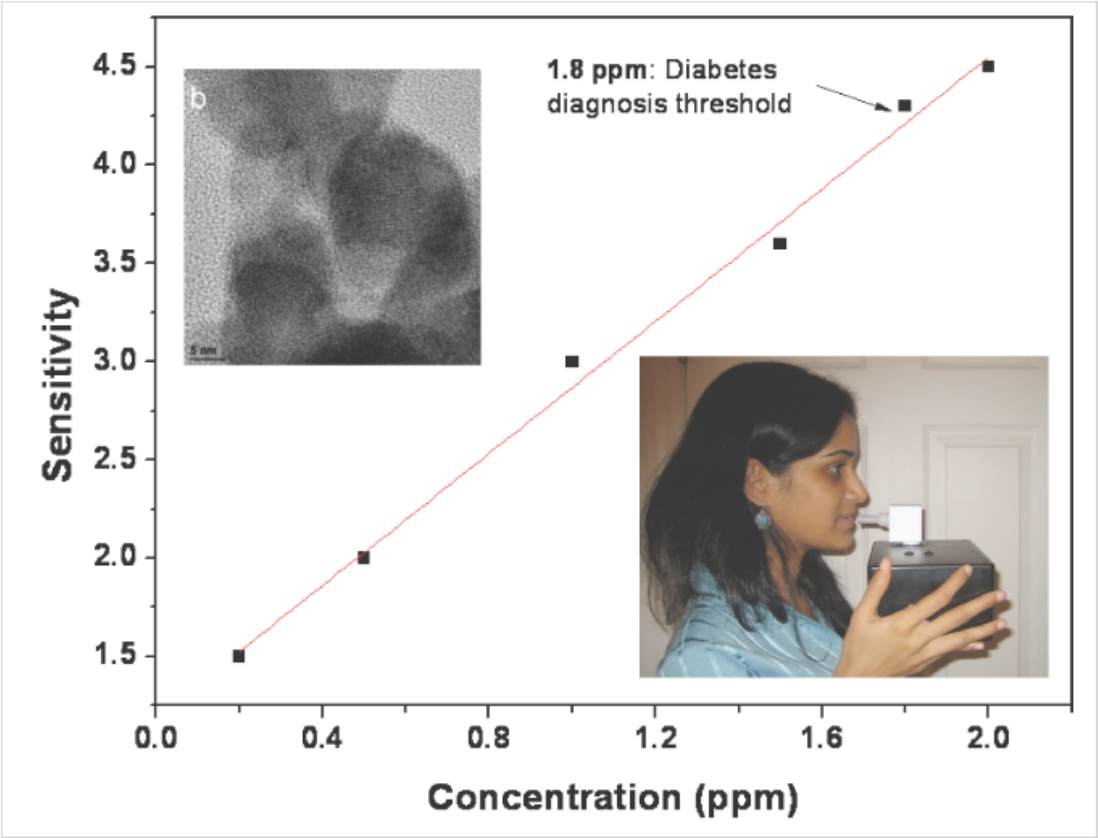


Figure 1: Plot illustrating linear sensor response in the range of acetone concentration relevant to diabetes detection, insets: b: nanoparticles of ferroelectric tungsten trioxide-based sensing element; and c: demonstrated use of the acetone breath-analyzer prototype.

Application #3: Hemodialysis Monitoring

Application:

- **Breath ammonia monitor that determines end-point in hemodialysis**
- consumer product for home use

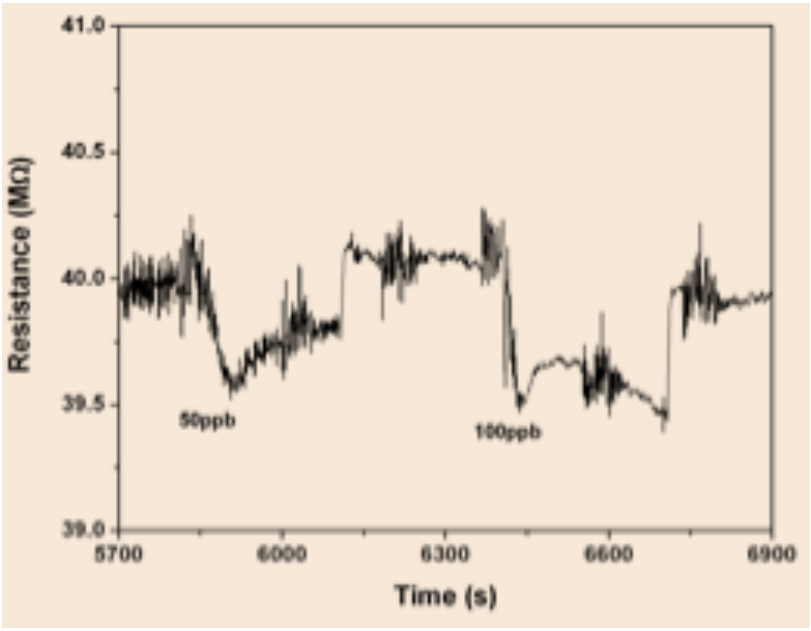
Biomarkers:

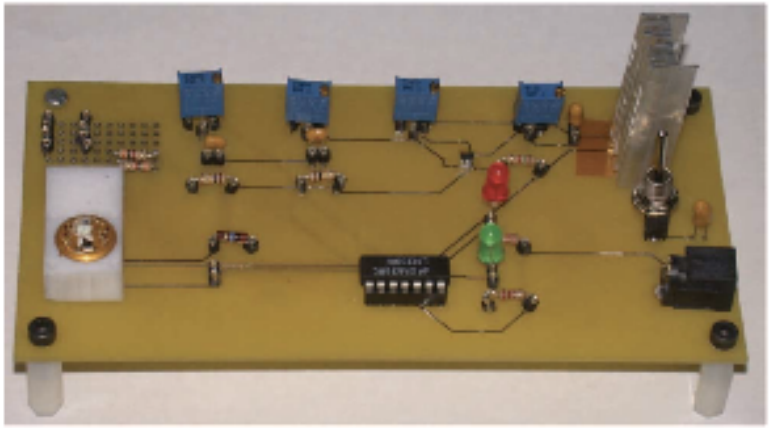
- Key biomarker**: ammonia** in breath
- in healthy individuals, ammonia turns to urea that is excreted into urine by the kidneys ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC31883/***
- Those suffering from renal failure have elevated amounts of ammonia in breath exhale
  - At the beginning of hemodialysis breath ammonia concentration is 1-2ppm
  - Towards the end is 150-200ppb

P. Gouma, Person. Med. , 8(1), pp. 15-16, 2011

Nanosensor and Breath Analyzer for Ammonia Detection in Exhaled Human Breath

Perena Gouma, Krithika Kalyanasundaram, Xiao Yun, *Student Member, IEEE*, Milutin Stanaćević, *Member, IEEE*, and Lisheng Wang



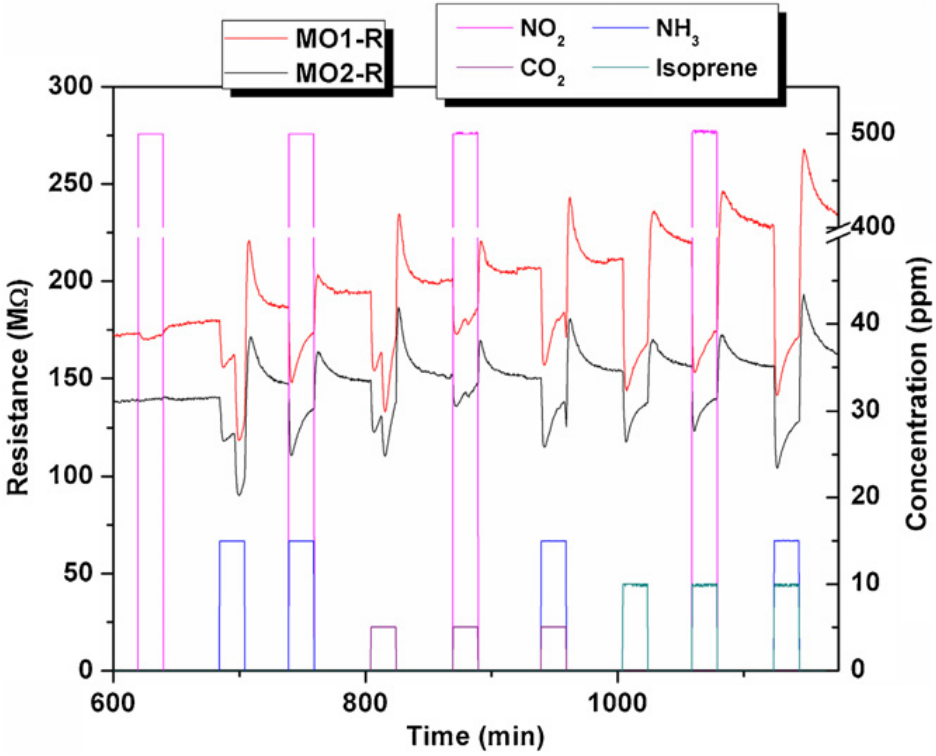


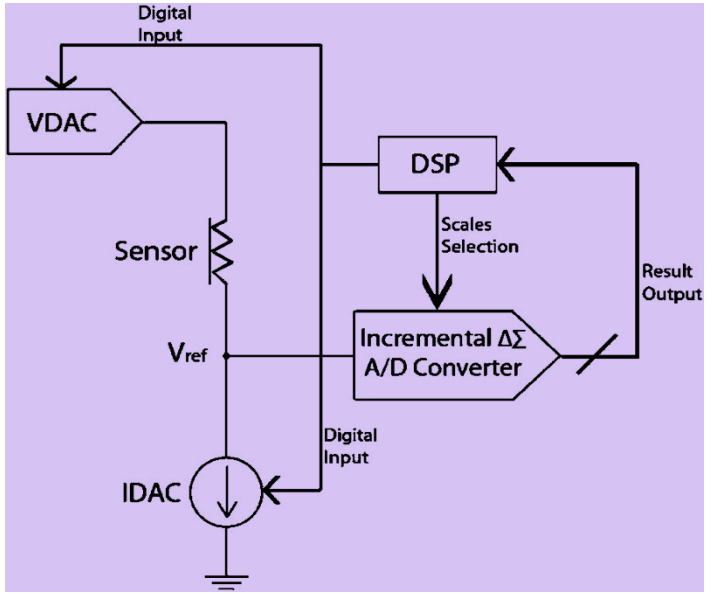
NANOSENSOR DEVICE FOR AMMONIA/UREA DETECTION IN EXHALED HUMAN BREATH

P. I. Gouma, US/Patent No 7,017,389 issued on 3/28/2006, "Sensors Including Metal Oxides Selective for Specific Gases and Methods for Preparing Same"

Breath Isoprene Monitoring Microsystem

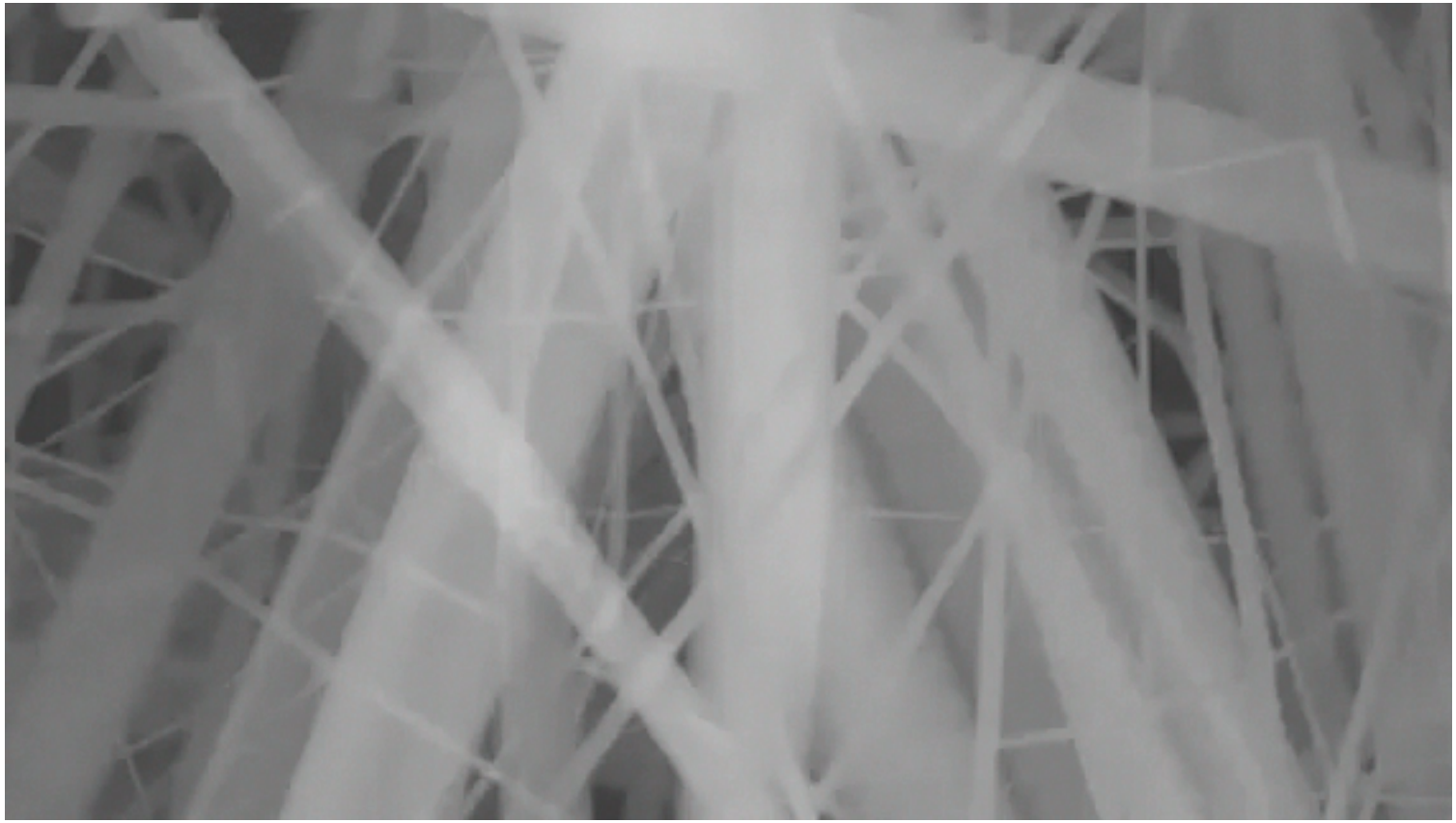
A selective nanosensor array device for exhaled breath analysis





P Gouma et al J. Breath Res. 5, 037110, 2011

TUNING THE BREATHALYZER FOR PATHOGEN DETECTION



http://www.nsf.gov/news/special_reports/science_nation/breathprinting.jsp

WEARABLE ACETONE MONITOR FOR DIET CONTROL

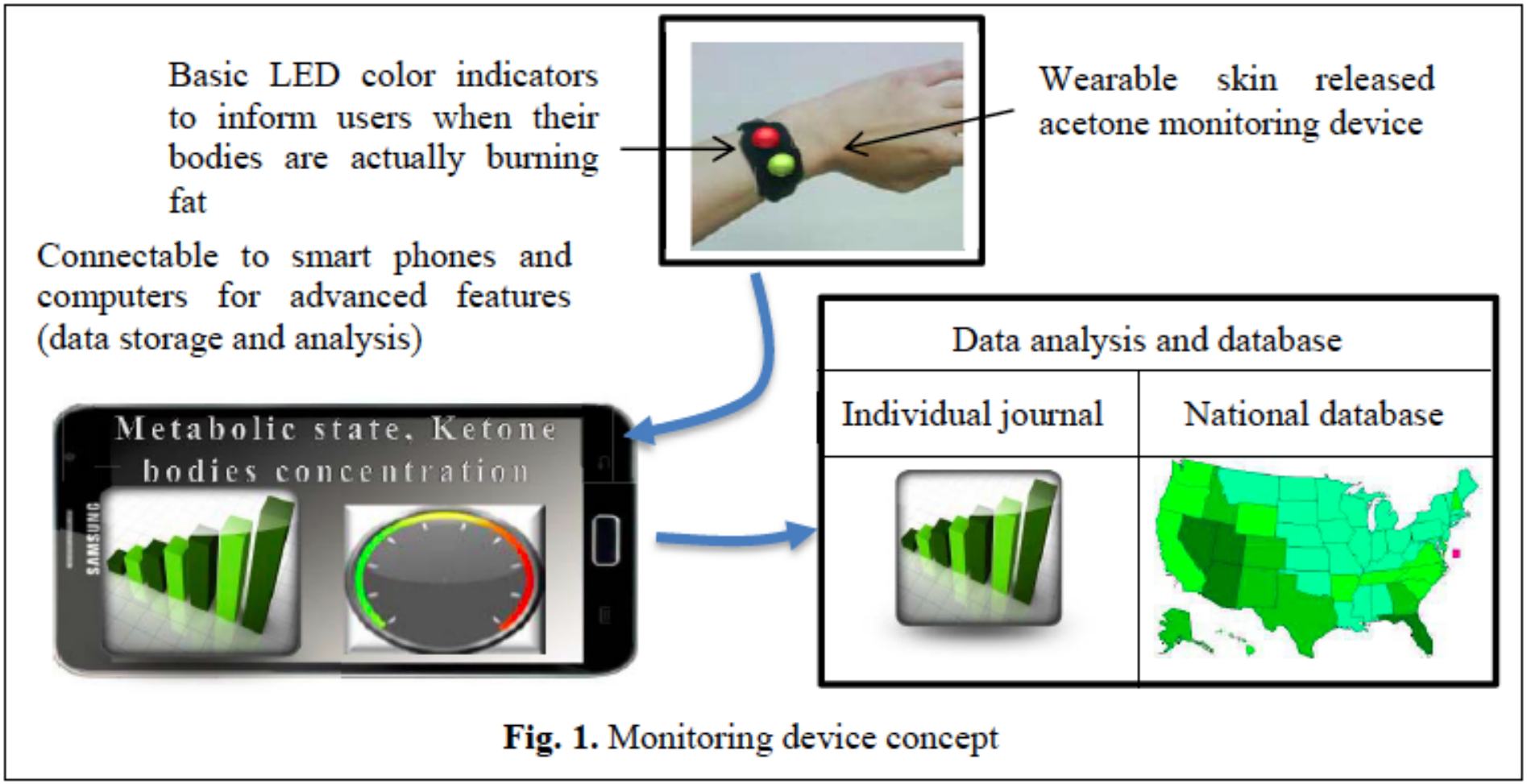


Fig. 1. Monitoring device concept

P. Gouma et al, "Metabolic Rate Monitoring and weight reduction/management", EMBC, 2014

Acknowledgments: P. Gouma wishes to thank the NSF, for support through several grants including: DMR-1106168 , IIS-1231761 and her research group through the years (especially, Drs. Arun Prasad, Krithika Kalyanasundaram, Aisha Bishop, and Lisheng Wang) and her collaborators Profs. Milutin Stanacevic (ECE) and Sandy Simon (SOM).

RELATED PRESS REPORTS

- **This Breathalyzer Reveals Signs of Disease (Science Nation)**
- **http://www.insidescience.org/content/cellphones-detecting-asthma/980**
- http://video.foxnews.com/v/1772104500001/bad-breath-a-sign-of-disease
- http://www.newsday.com/news/health/stony-brook-awarded-asthma-monitor-grant-1.4122040
- http://www.asthmaallergieschildren.com/2012/10/07/breathalyzer-for-asthma-nanotechnology-holds-promise-for-better-cheaper-monitoring-of-inflammation/
- http://www.northshoreoflongisland.com/Articles-Arts-and-Lifestyles-i-2012-10-11-93979.112114-sub-SBUs-Perena-Gouma-and-team-work-to-beat-asthma.html
- http://www.scientificamerican.com/article.cfm?id=electronic-nose-disease-diagnosis#comments