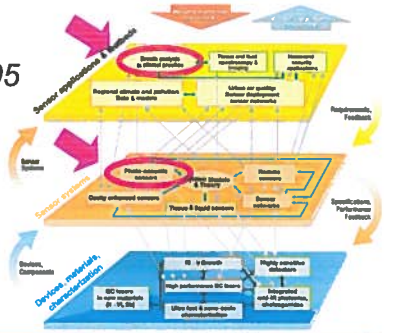
MIRTHE and Exhaled Human Breath Analysis for Clinical, Environmental and Homeland Security Applications

T.H. Risby,[1] S. Solga,[2] F.K. Tittel[3]

1 – Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD 21205

2– St. Luke's Hospital, 701 Ostrum St, Suite 604, Bethlehem, PA 18015

3 – Electrical and Computer Engineering Department, Rice University



History

- Water vapor has been used for centuries to detect the presence of life
- Classical medicine has used subjective impressions of odors of the body, i.e., sweat, urine, feces, and breath to diagnose disease
- Lavoisier first detected carbon dioxide in breath in 1784
- Earliest modern publications (Linus Pauling) on breath analysis date from the late 1960s early 1970s and mirror the development of modern analytical chemistry

Introduction

- Motivation: Mid-IR QCL sensor for trace gas detection in exhaled breath

Exhaled breath is an instantaneous mixture of molecules from the following sources

- molecules originating from inspiratory air
- molecules originating from dermal absorption
- molecules directly or indirectly derived from ingested food and beverages
- molecules produced by normal physiologies and can originate from tissues and cells throughout body

Breath composition will change as a function of breathing cycle

Breath molecules originate from cells throughout oral/nasal cavities, pulmonary system and cells and tissues throughout the organism

Breath composition will change with breathing physiology (hypo- or hyperventilation)

Typical concentrations of endogenous molecules found in breath

%	nitrogen, oxygen, carbon dioxide, water
ppm	acetone, carbon monoxide, methane, hydrogen
ppb	formaldehyde, acetaldehyde, isoprene, pentane, ethane, ethylene, nitric oxide, methanol, ethanol, carbonyl sulfide, methyl sulfide, ammonia, methylamine

Exhaled human breath could contain as many as 400 different molecules

Biochemical basis of major endogenous breath molecules

H_2	carbohydrate metabolism	CH_3CHO	ethanol metabolism
C_2H_5OH	gut bacteria	C_5H_{10}	cholesterol biosynthesis
H/C	lipid peroxidation metabolism	CH_3OH	fruit metabolism
CO	heme catabolism (HO1)	CH_3NH_2	protein metabolism
NO	nitric oxide synthase	C_2H_4	lipid peroxidation
C_5H_{12}	lipid peroxidation	$C_6H_{10}S$	garlic
C_2H_6	lipid peroxidation	CH_3SH	methionine metabolism
C_2H_6CO	decarboxylation of acetoacetate	CS_2	gut bacteria
		COS	gut bacteria
NH_3	protein metabolism	C_2H_6S	methionine metabolism
CH_4	carbohydrate metabolism		

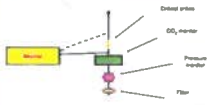
Endogenous breath molecules and mid IR detection

CH_3CHO	9.8-9.2 μm	C_5H_{12}	6.8 μm
C_5H_{10}	11.1 μm		
CH_3OH	9.7-8.5 μm	C_2H_6OH	9.8-9.2 μm
CH_3NH_2	12.2 μm	CO	4.7 μm
C_2H_4	10.6 μm	NO	5.3 μm
CH_3SH	3.45-3.28 μm	C_2H_6	6.8 μm
CS_2	6.5 μm	C_2H_6CO	7.3 μm
COS	4.8 μm	NH_3	10.3 μm
C_2H_6S	3.45-3.39 μm	CH_4	3.3 μm
		H_2S	1.6 μm

Do unique breath biomarkers exist?

- Unique biomarkers can only originate from the ingestion, inhalation, or absorption of foreign substances; or can only originate from the presence of bacteria, viruses, yeasts, moulds, or fungi,
- Normal and abnormal tissues will produce the same molecules: **abnormal physiologies will only change concentrations.**
- **Cellular biochemistry can only be induced, or suppressed by abnormal physiology.**
- Some disease states can appear to be producing unique molecules: **however these results are a reflection of the detection limit of the analytical method**

Reproducible single breath sampling



Controlled sampling based upon flow (pressure), and carbon dioxide

Preliminary clinical breath analysis

Clinical diagnosis	
airway reactivity	nitric oxide
oxidative stress	ethane, pentane
cholesterol biosynthesis	isoprene
renal function	ammonia
GI status	hydrogen, methane
liver function	ammonia, carbonyl sulfide, methyl sulfide, carbon monoxide
Infection	
metabolites	^{13}C carbon dioxide
host response to infection	carbon monoxide, ethane, nitric oxide

FDA approved breath tests

- Breath nitric oxide test to monitor therapy for asthma
- Breath carbon dioxide for capnography
- Breath hydrogen test for disaccharidase deficiency, gastrointestinal transit time, bacterial overgrowth, intestinal statis
- Breath carbon monoxide test for neonate jaundice and toxic exposure
- Urea $^{13}CO_2$ breath test for diagnosis of *H. pylori* infection
- Phillips hydrocarbon breath test for heart transplant rejection
- (Breath ethanol screening test for blood alcohol)

(red could be performed using a mid IR QCL
blue cannot be performed using a mid IR QCL)

Breath analysis and the human environment

- Exogenous compounds demonstrate uptake and bioavailable dose
- Timing and rates of biomarker concentrations demonstrate metabolic pathways (classical PK and PBPK)
- Timing and rates of biomarker concentrations demonstrate recent exposure profiles

Summary of studies to date

- Breath has been successfully used to estimate exposure to gasoline, jet fuel, inhalation anesthetics, and haloforms in the general population and in occupational exposed workers

Breath analysis and homeland security

- Breath can not be modified by an individual
- Breath may be collected surreptitiously even from a standoff
- Can be used to answer the following questions:
  - Where were you recently?
  - What were you doing?
  - Are you a threat?
- Future biomarker discoveries could enable the identification of those persons who have been in contact with biological weapons, explosive, or radioactive materials

Summary

- Breath analysis is non-invasive
- Breath can be collected multiple times without risk to the subject
- Children give breath samples willingly
- Breath can be collected from the neonate to the elderly (a mouse to an elephant)
- Breath can be easily collected in field, clinic, in-patient, OR and ICU
- The future of breath analysis for all applications is handheld devices that can respond to breath molecules faster than breathing frequency and that can provide results within 5 minutes
- Laser spectroscopy with a mid-infrared, room temperature, continuous wave, high performance QCL is a promising analytical approach for real time quantification of breath biomarkers

This material is based upon work supported by the National Science Foundation under Grant No. EEC-0540832.

www.mirthecenter.org