Advances in Optical Diagnostic Technologies in Medicine

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Houston, TX 77005
http://www.ece.rice.edu/lasersci/

- General Introduction to Lasers in Medicine and Life Sciences
- Motivation and Technology Issues for Non-invasive, Real-time Monitoring of Exhaled Human Breath
- Mid-Infrared Laser based Gas Sensor Platforms
- Examples of Breath Measurements: NO, CO and COS
- Summary and Outlook
Main Thrust of U.S. Laser Activities in 2005 and Beyond

1. Laser Devices
   New VUV to IR (Tunable Solid State) Lasers, Short Wavelength Lasers, Femtosecond Technology, High Power Lasers

2. Optical Communications and Information Technology (Photonics)
   Fiber Optics, Semiconductor Lasers, WDM Devices, Optical Data Storage (Holography)

3. Surface Engineering
   Integrated Optics, Microelectronics (Photolithography)
4. Industrial Applications

5. Medical and Biomedical Applications


7. Photophysics
   Quantum Optics, Nonlinear Optical Processes, Laser Fusion, Nanotechnology

8. Laser Chemistry
   Chemical Reactions and Kinetics, Combustion, Isotope Separation
Unique Properties of Laser Light

• Intensity
• Monochromaticity (Coherence)
  ▪ Spectral Resolution
  ▪ Temporal Resolution
• Directionality
• Wavelength Tunability
• Efficiency
Electromagnetic Spectrum (X-ray to THz)
Laser Types

- Lasers can have different:
  - Lasing media (gases, solids, semiconductors, liquids)
  - Mode of pumping (optical, discharge, electrical, chemical)
  - Output mode (pulsed, cw, quasi cw)
  - Wavelengths (from XUV to far-IR)

- Important laser types include:
  - Semiconductor diodes
  - Nd: glass, Nd:YAG, Ti: sapphire
  - Carbon dioxide, Excimer
Motivation & Technology Issues for Optical Diagnostic Technologies in Medicine
Applications of Optical Diagnostic Technologies in Medicine and the Life Sciences - Biophotonics

- **Breath Analysis**
- **Lasers in Ophthalmology**
- **Cancer Diagnostics and Therapy**
- **Bio-imaging applications: Scattering Spectroscopy & Tissue Trans-illumination**
- **Tissue Engineering**
- **Applications in the Life Sciences**
  - Laser manipulation – laser tweezers
  - Energy Transfer in DNA Complexes
  - Correlation Spectroscopy in Microbe Movements
In vivo OCT tomograms (a) and with (b) adaptive optics. The use of adaptive optics increases the transverse resolution of the OCT image to $5-10 \ \mu m$, and improves the signal to noise ratio by up to 9 dB.
Effect of Air Pollution – NO\textsubscript{X}

- Ambient nitric oxide (aNO) is a major component of smog.
  - Automobile exhaust is a primary source.
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Source: United Nations

- High pollution
- Moderate to heavy pollution
- Low pollution
- No data available
Volcanological applications

- CO$_2$ the most abundant component of volcanic gases after H$_2$O
- $\delta^{13}$C is a sensitive tracer of magmatic vs. hydrothermal or groundwater contributions to volcanic gases
- Monitoring $\delta^{13}$C can be used in eruption forecasting and volcanic hazard assessment
Hippocrates considered the odor of exhaled breath an important tool in diagnosing diseases.
Motivation of laser based breath analysis

• Exhaled breath biomarkers have diagnostic and therapeutic potential. Breath biomarkers have particular clinical appeal because they are:
  ▪ Non-invasive
  ▪ Repeatable or continuous
  ▪ Real-time
  ▪ Applicable as markers of many diseases, exposure & susceptibility
What is breath?

- Any molecule that has a measurable vapor pressure can be present in exhaled breath
- Breath is a reflection of composition of inspiratory air and endogenously produced molecules
- Sampling breath is non-invasive; can be collected from mouse to man, and from neonate to elderly
- Can sample breath temporally without exposing subject to any risk
Composition of exhaled breath

• **Bulk matrix** (99.99999%)
  - Nitrogen
  - Oxygen
  - Water
  - Carbon dioxide
  - Inert gases

• **Trace components** (<1ppm)
  - Endogenous molecules
  - Exogenous molecules
Trace components of breath

- Approximately 300 compounds have been identified in breath
  - Endogenous origins
    - Ethane (0-10 ppb), pentane (0-10 ppb), isoprene (50-200 ppb), acetone (0-1 ppm), ethylene, ethanol, methanol, acetaldehyde, isopropanol, carbon monoxide (0-10 ppb), nitric oxide (1-50 ppb), sulfides, amines, ammonia (0-1 ppm),
  - Exogenous origins
    - Reflection of the composition of inhaled air: indoor and outdoor pollution
    - Reflection of prior consumption of foods, or beverages
  - Typically [exogenous]>[endogenous]
## Important Biomedical Target Gases

<table>
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<tr>
<th>Molecule</th>
<th>Formula</th>
<th>Biological/Pathology Indication</th>
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<tbody>
<tr>
<td>Pentane</td>
<td>CH$_3$(CH$_2$)$_3$CH$_3$</td>
<td>Lipid peroxidation, oxidative stress associated with inflammatory diseases, transplant rejection, breast and lung cancer</td>
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<td>Ethane</td>
<td>C$_2$H$_6$</td>
<td>Lipid peroxidation and oxidative stress</td>
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<td>CO$_2$ isotope ratio</td>
<td>$^{13}$CO$_2$ / $^{12}$CO$_2$</td>
<td>Marker for Heliobacter pylori infection, Gastrointestinal and hepatic function</td>
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<td>Carbonyl Sulfide</td>
<td>COS</td>
<td>Liver disease and acute rejection in lung transplant recipients (10-500 ppb?)</td>
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<tr>
<td>Carbon disulfide</td>
<td>CS$_2$</td>
<td>Schizophrenia</td>
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<td>Ammonia</td>
<td>NH$_3$</td>
<td>Hepatic encephalopathy, liver and renal diseases, fasting response</td>
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<td>Formaldehyde</td>
<td>HCHO</td>
<td>Cancerous tumors, breast cancer (400-1500 ppb)</td>
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<td>Nitric Oxide</td>
<td>NO</td>
<td>Inflammatory and immune responses (e.g., asthma) and vascular smooth muscle response (6-100 ppb)</td>
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<td>Hydrogen Peroxide</td>
<td>H$_2$O$_2$</td>
<td>Airway Inflammation, Oxidative stress (1-5 ppb)</td>
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<tr>
<td>Carbon Monoxide</td>
<td>CO</td>
<td>Smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation (400-3000 ppb)</td>
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<tr>
<td>Ethylene</td>
<td>H$_2$C=CH$_2$</td>
<td>Oxidative stress, cancer</td>
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<tr>
<td>Acetone</td>
<td>CH$_3$COCH$_3$</td>
<td>Fasting response, diabetes mellitus response, ketosis</td>
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**Exhaled NO and CO in Diseases**

### Exhaled Nitric Oxide
- Asthma
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchiectasis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Pulmonary hypertension
- Occupational diseases
- Infections
- Chronic cough
- Lung cancer
- Lung transplant rejection
- Adult respiratory distress syndrome
- Diffuse Panbronchiolitis

### Exhaled Carbon Monoxide
- Asthma
- Chronic obstructive pulmonary disease
- Bronchiectasis
- Cystic fibrosis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Allergic rhinitis
- Infections
- Smoking status

### Non-lung conditions
- Systemic inflammation in critical care patients
- Diabetes (hyperglycemia)

Maternal cigarette smokers

The graph shows the comparison between smokers and non-smokers in terms of ethane pmol/kg.min. The y-axis represents ethane pmol/kg.min, ranging from 0 to 4. The x-axis categorizes the participants into smokers and non-smokers. The graph indicates a higher ethane pmol/kg.min level in smokers compared to non-smokers.
Neonates of mothers that smoke

![Graph showing ethane pmol/kg.min for smokers (FF), smokers (BF), non-smokers (FF), and non-smokers (BF).]
Aircrafts at Warfield ANG, MD

A-10 Warthog

C-130
• **Goal:**
  - To quantify individual exposure to JP-8 and correlate JP-8 exposure with adverse health effects

• **Requirements:**
  - Provide a breath sample before work (pre)
  - Provide a breath sample after work (post)

  - Breath was used to quantify exposure and potential effects of JP-8 exposure hydrocarbons, CO, NO, and sulfur-containing compounds
Human Subject Exposed to JP-8

DAV6850 Pre-Exposure

DAV6850 Post-Exposure
How does Exposure Compare Among Military Bases?

Total JP-8 Base Comparison

Air Force Exposed

Air National Guard Exposed

Air Force Incidental

Air National Guard Incidental

[JP-8] (mg/m³)

0

20

40

60

80

100
Study design of breath analysis from rats based on diet

B  three weeks  B

A  eight weeks

B  eight weeks

C  eight weeks

X  Baseline sampling  X  End of study sampling
### Diet (%) for exhaled ethane from rats

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<th>C</th>
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<td>Fruits/Vegs</td>
<td>100 g/day</td>
<td>500 g/day</td>
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Change in breath ethane from baseline to end of study

-1.5 ppb
0.0 ppb
+1.5 ppb

Diet A
Diet B
Diet C

CHANGE IN BREATH ETHANE
Laser Absorption Spectroscopy
Existing Methods for Trace Gas Detection

Non-Optical
- Mass Spectroscopy
- Chemical
- Electro Chemical

Optical
- Non-Dispersive
  - Chemiluminescence
  - Fourier Transform
  - Gas Filter Correlation
  - Microwave Spectroscopy
- Dispersive
  - Laser Spectroscopy
- Gas Chromatography
Tunable Diode Laser Absorption Spectroscopy (TDLAS)

Molecules absorb infrared light:

- $\lambda_1$
- $\lambda_2$
- $\lambda_3$
CW IR Source Requirements for Laser Spectroscopy

**REQUIREMENTS**
- Sensitivity (% to ppt)
- Selectivity
- Multi-gas Components
- Directionality
- Rapid Data Acquisition
- Room Temperature
- Field deployable

**IR SOURCE**
- Power
- Narrow Linewidth
- Tunable Wavelengths
- Beam Quality
- Fast Time Response
- No Consumables
- Compact & Robust
Molecular Absorptions and Laser Sources

QC lasers (pulsed with TEC, CW with cryogenic cooling and TEC; high output power)

Diodes + PPLN, P~1-10 µW → 1mW

DFG and OPO

Room temperature

DIODE LASERS

QPM GaAs (available in future)

Cryogenic (P<1 mW)

To ~160 µm

Wavelength, µm
Sensitivity Enhancement Techniques

- **Optimum Molecular Absorbing Transition**
  - Overtone or Combination Bands (NIR)
  - Fundamental Absorption Bands (MID-IR)

- **Long Optical Pathlength**
  - Multipass Absorption Cell (White, Herriot)
  - Cavity Enhanced and Cavity Ringdown Spectroscopy
  - Open Path Monitoring (with retro-reflector)
  - Fiberoptic Evanescent Wave Spectroscopy

- **Spectroscopic Detection Schemes**
  - Frequency or Wavelength Modulation
  - Balanced Detection
  - Zero-air Subtraction
  - Photoacoustic Spectroscopy
  - Noise Immune Cavity Enhanced-Optical Heterodyne Molecular Spectroscopy (NICE-OHMS)
Laser Absorption Spectroscopy (LAS) for Breath Analysis

- LAS based sensors can realize sensitive, selective and fast concentration measurements of specific medically relevant target gases (e.g. NO, CO & COS)
- LAS is capable of detecting and quantifying multiple gas species with a single laser which is important for standardizing exhaled breath analysis data
- Lasers make it possible to design compact, portable, robust and autonomous LAS based sensors
Nitric Oxide (NO) Detection
The Nobel Prize in Physiology or Medicine 1998

Robert F. Furchgott
1/3 of the prize
USA

Louis J. Ignarro
1/3 of the prize
USA

Ferid Murad
1/3 of the prize
USA

SUNY Health Science Center
Brooklyn, NY, USA

b. 1916

University of California School of Medicine
Los Angeles, CA, USA

b. 1941

University of Texas Medical School at Houston
Houston, TX, USA

b. 1936
Nitric oxide: Various Human Functions

- **Blood vessels**: NO dilates blood vessels and lowers the blood pressure.
- **Colon**: NO kills hostile bacteria.
- **Respiratory tract**
- **Immune system**: NO kills hostile bacteria.
- **Brain**: learning and remembering.
- **Enzymes produce NO**
- **Neurotransmitter**
Nitric Oxide Breath Sensor

Self-calibrating sensor
Patient’s own exhaled CO₂ is the calibration gas
Why Adopt eNO Analysis

• 17 million Americans have asthma
• Asthma is the #1 chronic disease among children
• Asthma rates are increasing at near epidemic rates
• No routine point-of-care clinical procedures to assess lower airway inflammation
• NAEPP Guidelines are not widely followed
• When properly managed
  • 78% reduction in hospitalizations
  • 73% reduction in emergency room visits

“Under-treatment of inner-city asthma is the rule rather than the exception”,

Dr. Kristin Riekart, Johns Hopkins
eNO and eCO₂ Trends

Single Exhalation Against Resistance (10-20 sec)

eNO = 8.9 ppb

Time (seconds)

End-Tidal CO₂

Nasal NO

eNO

Begin Exhalation

End Exhalation
Advantages of Simultaneous exhaled NO and CO$_2$

- Verify Correct Breath Donations
- Determine eNO Concentrations
- Serves as Internal Indicator of Instrumental Factors

We can now deduce *instrumental* vs. *physiological*
End-tidal CO$_2$ can be used to determine eNO levels and can account for variations in exhalation maneuvers between patients.

Nasal NO Contamination

End-tidal CO$_2$ can be used to determine eNO levels and can account for variations in exhalation maneuvers between patients.

Nasal NO Contamination
Sources of NO and CO

- **Airway Epithelial Cell**
  - NOS + L-arginine

- **Most cells**
  - HO + Hemoglobin

**Conducting airway**
- NO

**Dead space**

**Alveolar region**
- CO

**Pulmonary Blood**
- CO
Point of Care
Exhaled Nitric Oxide Instrumentation

• **Chemiluminescence (Aerocrine & Sievers)**
  - Used for over ten years to measure eNO in both children and adults
  - FDA approval has been granted, March 2003 (product code MXA)
  - Inter-study reproducibility issues
  - Requires calibration at same humidity and temperature as breath
  - Issues regarding explosive reactions to anesthesia
  - Three consumables: clean air, ozone, and NO calibration gas

• **TDLAS**
  - Used to measure eNO in both children and adults
  - Demonstrated internal-calibration using exhaled CO₂ levels
  - No consumables
Asthmatic Examples

Age 5, Female, Mild-Persistent Corticosteriod Treated

Normal Airway

eNO = 8.9 ppb

Age 14, Male, Mild-Persistent Non-Treated

Inflamed Airway

eNO = 52.9 ppb

Time (seconds)
eNO (ppb)
eCO2 (%)
Therapy Monitoring

![Graph showing eNO (ppb) levels over days for a Corticosteroid Treated Patient and a Nonasthmatic Volunteer.](image)

- **Corticosteroid Treated Patient**
- **Nonasthmatic Volunteer**

The graph illustrates the eNO (ppb) levels over days for both groups. It shows a significant decrease in eNO levels for the Corticosteroid Treated Patient starting from day 8 onwards, indicating the effectiveness of the therapy.

**Started Inhaled Glucocorticoid Therapy**
“Physicians need to diagnose asthma early and accurately… Untreated inflammation leads to more severe symptoms, airway injury, and a worse long-term prognosis.”
*S. F. Steinbach, M.D.*, *Contemporary Pediatrics*, October 2000

“Officials in many school systems estimate… asthma among their students at 3% to 4%. But a number of studies… suggest the correct number is closer to 15%”,
*R. L. Wolf, M.D.*, Associate Professor of Pediatrics, University of Chicago.
*M. Pinkowish, Patient Care*, Feb 15, 2000
Current Research

- TDLAS offers robust and routine measurement of lower airway eNO.
- The breath donation procedure is simple, rapid, non-invasive, and suitable for children and adults.
- eNO can be useful as a marker for lower airway inflammation and overall respiratory health in populations.
- Currently conducting clinical research in collaboration with the American Lung Association.
- Want to examine large social issues associated with asthma.
Cavity Enhanced Spectroscopy of Breath Samples

- Advanced compact gas cell design
- Capable of cell volumes < 100 cm³
- Enables rapid measurements of eNO for flow independent eNO analysis
- Can distinguish between NO originating from airway walls or alveolar regions
- Useful in differentiating between asthma and alveolitis
Ultra-sensitive Absorption Spectroscopy Techniques

Traditional

1. Multipass cell spectroscopy

Capable of Compact Gas Cells

2. Cavity Ringdown Spectroscopy (CRDS)

3. Integrated Cavity Output Spectroscopy (ICOS)
Off-Axis Integrated Cavity Output Spectroscopy Based Gas Sensor

- Novel compact gas cell design of length: 3.8 – 5.3 cm and cell volumes < 80 cm³;
- Low loss mirrors (ROC 1m): ~60-250 ppm, R~99.975, L_eff =170-800 m
- Rapid eNO concentration measurements during a single breath cycle are feasible
Off-axis ICOS Detection of NO at 1920.7 cm$^{-1}$

- 95 and 490 ppb NO/N$_2$ calibration mixture at 100 Torr total pressure
- Effective optical path $\sim$ 70 m (1,350 passes)

Noise-equivalent sensitivity is 10 ppb for 1$\sigma$ deviation of the best fit coefficient.
Detection sensitivity: $1.0 \times 10^{-7}$ cm$^{-1}$ Hz$^{-1/2}$

- Voigt fit of measured NO absorption line at 1920.7 cm$^{-1}$ for a concentration of 95 ppb
NO from Nasal Exhaled Air
(OA-ICOS and wavelength modulation spectroscopy)

Medically approved collection bag for human breath samples

Averaged 2f signal of the OA-ICOS cavity output

(1) Nasal NO concentration: 53 ppb
(2) 95 ppb NO/N₂ calibration mixture
IV

Carbon Monoxide (CO) Detection
Exhaled NO and CO in Diseases

Exhaled Nitric Oxide

- Asthma
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchiectasis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Pulmonary hypertension
- Occupational diseases
- Infections
- Chronic cough
- Lung cancer
- Lung transplant rejection
- Adult respiratory distress syndrome
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Exhaled Carbon Monoxide

- Asthma
- Chronic obstructive pulmonary disease
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- Rhinitis
- Interstitial lung diseases
- Allergic rhinitis
- Infections
- Smoking status

Non-lung conditions

- Systemic inflammation in critical care patients
- Diabetes (hyperglycemia)

Carbon Monoxide (CO) Sensor Architecture

MPC – 100 m Multipass Herriott Cell
M – Mirror
L – Lens
PM – Off Axis Parabolic Mirror
BS – Beam Splitter
QCL – Quantum Cascade Laser

- Sample Beam
- Reference Beam
Motivation for DSP

• Portability and Integration
  ▪ Field campaigns
  ▪ Sensor networks
• Advanced control of system
  ▪ Modulation and feedback
• Fast data acquisition
  ▪ Co-averaging of spectra for lower detection limit
• Faster processing
  ▪ Polynomial fitting routines
  ▪ Fast multiply-accumulate for filtering
• Low power
  ▪ Battery powered sensors
DSP System Controller Card

- Compact for clinical/hospital use
- Dimensions: 5.35 in x 3.00 in x 1.50 in
- Ethernet, Serial, JTAG access for control and read out
- Flash memory for long term storage
- PC independent operation
- Up to 12.5 MSPS 12-bit ADC
Exhaled CO from a Non-Smoker

- 10 second breath holding increases the exhaled CO concentration.

\( C_{\text{CO}} = 2.7 \text{ ppm} \)

\( C_{\text{CO}} = 2.3 \text{ ppm} \)
Exhaled CO from a Smoker

### 10s Breath Hold Absorption Spectrum

<table>
<thead>
<tr>
<th>Channel Number</th>
<th>Signal (Arb Units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.94</td>
</tr>
<tr>
<td>500</td>
<td>0.98</td>
</tr>
<tr>
<td>1000</td>
<td>1.02</td>
</tr>
</tbody>
</table>

### Continuous Breath Sampling Absorption Spectrum

<table>
<thead>
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<th>Channel Number</th>
<th>Signal (Arb Units)</th>
</tr>
</thead>
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<tr>
<td>0</td>
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</tr>
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<td>0.94</td>
</tr>
</tbody>
</table>

\[ C_{CO} = 1.4 \text{ ppm} \]

\[ C_{CO} = 1.0 \text{ ppm} \]

- 10 second breath holding increases the exhaled CO concentration.
- Environmental conditions and time since last cigarette appear to significantly affect exhaled CO concentration.
QC laser-based measurements of CO trace gas above cell cultures

- Measured CO production rates of viable cultures of vascular smooth muscle cells
- Achieved a detection limit of for CO of ~20 ppb
Measured CO production above cultured cells compared to control measurements without cell cultures

Important in the understanding of kinetic or time dependent production of CO in heme catabolism

CO Production Rate
~ 44 ppb/h
V

Carbonyl Sulfide (OCS) Detection
Motivation for OCS detector design

• Breath analysis is a non-invasive way of human disease detection

• Elevated COS concentrations in exhaled breath have been reported in lung transplants recipients suffering from acute rejection

  S.M. Studer et al., “Patterns and Significance of Exhaled-Breath Biomarkers in Lung Transplant Recipients with Acute Allograf Rejection”, J. of Heart and Lung Transplant, 20(11), 1158 (2001)

• As well as in patients with liver disease


• Application of quantum-cascade (QC) lasers allows the design of a compact sensitive, and selective trace-gas sensor

• Goal: non-invasive rapid, *in situ* detection of trace-gases in exhaled human breath
A 2001 study by the T. H. Risby group at John Hopkins University demonstrated that elevated levels of COS could have a diagnostic role in the detection of acute allograft rejection in lung transplant recipients.


Measured with gas chromatography and flame ionization detection.
OCS ro-vibrational $\nu_3$ spectrum at $\sim 4.85\mu$m

- OCS line intensity:
  - $7.49 \cdot 10^{-19} \text{ cm}^{-1}/\text{molecule}\cdot\text{cm}^2$
- Minimal spectral interference by nearby CO$_2$ and H$_2$O absorption lines
- Availability of a CO$_2$ line within the fast tuning range of the QCL for ventilation monitoring simultaneously with an OCS measurement
OCS Sensor Architecture

**Components:**
- PULSED QCL DRIVER
- SB – Sample beam
- RB – Reference beam
- LH – Laser housing
- CL – Collimating lens
- BS – Beam splitter
- M – Mirror
- PM – Off-axis parabolic mirror
- GATE GENERATOR
- TRACK & HOLD’s
- REFERENCE
- SAMPLE
- TRIGGER PULSE GENERATOR
- FUNCTION GENERATOR
- PC
- DAQ CARD
- NI 6062E
- PCMCT

**Abbreviations:**
- QCL – Quantum cascade laser chip
- LH – Laser housing
- CL – Collimating lens
- SB – Sample beam
- RB – Reference beam
- M – Mirror
- BS – Beam splitter
- PM – Off-axis parabolic mirror

**Image Credit:**
Monitoring breathing

- **Single breath**
  - Control expiratory flow
  - Control mouth pressure
  - Monitor concentration of carbon dioxide

- **Multiple breaths**
  - Measure flow
  - Monitor frequency
  - Monitor mouth pressure
  - Monitor concentration of carbon dioxide
Breath Collector Configurations

**Single Breath**

- Mouthpiece
- Biological Filter
- Pressure Meter
- Flow Meter
- Discard Volume
- PSI Card
- Tedlar bag
- Gas Cell

**Continuous Breathing**

- Mouthpiece
- Biological Filter
- Pressure Meter
- Unidirectional Tee
- Discarded
- Flow Meter
- PSI Card
- Vacuum Container
- Tedlar bag
- Pump
- Gas Cell
OCS Concentration Calibration of QCL Sensor

Calibration curve

$
\begin{align*}
0.27 \text{ ppb} \cdot \sqrt{1000/100} &= 0.85 \text{ ppb} \\
\text{Scattering of the concentration measurement: } \sigma &= 1.2 \text{ ppb}
\end{align*}$

1000 spectra averaged acquired within $t = 4 \text{ s}$ and fitted to 300 ppb OCS reference spectrum

100 spectra averaged acquired within $t = 0.4 \text{ s}$ and fitted to 300 ppb OCS reference spectrum
OCS and CO$_2$ Concentration Measurements in Exhaled Breath

- Sample was taken from lung transplant patient suffering from bronchiolitis*
- Sampling was performed using chemically inert 1 liter tedlar sampling bags and analyzed within 2 hours after collection
- Spectrum was measured at a total pressure of 60 torr

* The authors wish to thank Dr. Remzi Bag and Carolyn M. Paraguaya from Baylor College of Medicine, Houston, TX for supplying breath samples
Schematic of a Portable LAS System

- QC Laser Housing
- Laser Driver
- Pulse Generator
- Pump
- Gas Cell
- 0.5 meters
- Power Supply
- DAQ System
Thermal Gas Desorption Tube

Adsorption

Adsorbent 1

Adsorbent 2

Desorption
VI

Emerging Optical Technologies in Medicine
## Important Biomedical Target Gases

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formula</th>
<th>Biological/Pathology Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentane</td>
<td>$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$</td>
<td>Lipid peroxidation, oxidative stress associated with inflammatory diseases, transplant rejection, breast and lung cancer</td>
</tr>
<tr>
<td>Ethane</td>
<td>$\text{C}_2\text{H}_6$</td>
<td>Lipid peroxidation and oxidative stress</td>
</tr>
<tr>
<td>$\text{CO}_2$ isotope ratio</td>
<td>$^{13}\text{CO}_2 /^{12}\text{CO}_2$</td>
<td>Marker for Heliobacter pylori infection, Gastrointestinal and hepatic function</td>
</tr>
<tr>
<td>Carbonyl Sulfide</td>
<td>$\text{COS}$</td>
<td>Liver disease and acute rejection in lung transplant recipients (10-500 ppb?)</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>$\text{CS}_2$</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Ammonia</td>
<td>$\text{NH}_3$</td>
<td>Hepatic encephalopathy, liver and renal diseases, fasting response</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>$\text{HCHO}$</td>
<td>Cancerous tumors, breast cancer (400-1500 ppb)</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>$\text{NO}$</td>
<td>Inflammatory and immune responses (e.g., asthma) and vascular smooth muscle response (6-100 ppb)</td>
</tr>
<tr>
<td>Hydrogen Peroxide</td>
<td>$\text{H}_2\text{O}_2$</td>
<td>Airway Inflammation, Oxidative stress (1-5 ppb)</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>$\text{CO}$</td>
<td>Smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation (400-3000 ppb)</td>
</tr>
<tr>
<td>Ethylene</td>
<td>$\text{H}_2\text{C}=\text{CH}_2$</td>
<td>Oxidative stress, cancer</td>
</tr>
<tr>
<td>Acetone</td>
<td>$\text{CH}_3\text{COCH}_3$</td>
<td>Fasting response, diabetes mellitus response, ketosis</td>
</tr>
</tbody>
</table>
Background of Helicobacter Pylori

• *Helicobacter Pylori* is a common bacteria infecting over 50% of the world’s population
  ▪ Incidence of infection decreases in developed countries (e.g. good sanitation = less infections)
• Risk of peptic and gastric ulcers increased tenfold in patients infected with H. Pylori
  ▪ Over 4 million people in the US, accounting for over $5 billion annually
H. Pylori
Laser based Photoacoustic Spectroscopy

Traditional PAS:
Resonant cell, broadband microphone
Cell dimensions \((\text{sound wavelength})/2\)

\[ S_{\text{PAS}} \sim \frac{Q\alpha P}{fV} \]

Wavelength modulation and \(2f\) detection

QEPAS:
Piezoelectric quartz crystal, optional cell

\[ S_{\text{QEPAS}} \sim \frac{Q\alpha P}{f} \]

Sensitivity \([k] = \frac{\text{cm}^{-1} \times \text{W}}{\sqrt{\text{Hz}}}\)

 WATCH CRYSTAL TUNING FORKS

Frequency: 32.768kHz ±30ppm. Operating temperature: -10°C to +60°C.
ESR: 35kHz max. (R26), 50kHz max. (R38)
Comparative Size of Absorbance Detection Modules (ADM)

Optical multipass cell (100 m):
l~70 cm, V~3000 cm³

Resonant photoacoustic cell (1000 Hz):
l~60 cm, V~50 cm³

QEPAS ADM:
l~0.5 cm, V~0.05 cm³
Calibration and Linearity of QEPAS based NH$_3$ Sensor

Noise-equivalent (1s) concentration (NEC). for $\tau=1s$ time constant is 0.65 ppmv for 38 mW excitation power.

Noise-equivalent absorption (NEA) coefficient $k=7.2\times10^{-9}$ cm$^{-1}$W/Hz$^{1/2}$

*Webber et al., APPLIED OPTICS April 2003 Vol. 42, No. 12, p.2119

90 last points of each step averaged

(Traditional PAS* – 1.5$\times$10$^{-9}$ cm$^{-1}$W/√Hz)
Merits of QE Laser-PAS based Trace Gas Detection

- Immune to ambient and flow acoustic noise, laser noise and etalon effects
- Dramatic reduction of sample volume (< 1 mm$^3$)
- High sensitivity (ppm to ppb gas concentration levels) and excellent dynamic range
- Applicable over a wide range of pressures
- Temperature, pressure and humidity insensitive
- Rugged and low cost compared to LAS that requires a multipass absorption cell and infrared detector(s)
- Potential for optically multiplexed concentration measurements
Summary and Future Directions

- **Quantum Cascade Laser based Trace Gas Sensors**
  - Compact, tunable, and robust designs can be realized
  - High sensitivity ($<10^{-4}$) and selectivity (3 to 300 MHz)
  - Fast data acquisition and analysis
  - Detected trace gases: NH$_3$, CH$_4$, N$_2$O, CO$_2$, CO, NO, H$_2$O, COS, C$_2$H$_5$OH and isotopic species (C,O,S)

- **Medical Applications in Exhaled Breath Analysis**
  - eNO: many lung diseases such as asthma and alveolitis (e.g. interstitial pneumonia or idiopathic pulmonary fibrosis)
  - COS: lung transplant rejection & liver diseases
  - eCO: pulmonary diseases, neonatal non-hemolytic hyperbilirubinemia, diabetes

- **Future Directions**
  - Develop advanced gas sensor for eNO and COS detection
  - Place a robust and portable point-of-care mid-IR laser based gas sensor in a clinical setting
  - Investigate other gas phase biomarkers of human diseases