Photonic Technologies for Early Detection of Human Disease

Principal Investigator: Dr. Mark Allen
Physical Sciences Inc.
Co-Investigator: Dr. Frank Tittel
Rice University [http://www.ece.rice.edu/laserSci/]
Co-Investigator: Dr. Tony O’Keefe
Los Gatos Research

Presentation Outline

- Motivation and Background for Physiological Monitors based on Expired Human Breath
- Target Trace Gases and Pathologies
- Ultra-Sensitive Gas Detection based Quantum Cascade Laser (QCL) Absorption
- Examples of QCL-based Breath Measurements
- Program Plan and Status

Trace Reactive Gases As Physiological Messengers

- NO production is tied to numerous physiological processes:
  - vasorelaxation, inflammation, thrombosis, immunity
  - reduced NO production associated with atherosclerotic and ulcers
  - enhanced NO production associated with asthma, endotoxin shock, diabetes, and health
- CO production is important in vascular muscle cell physiology and platelet aggregation
- Trace levels of NO and other breath species are associated with numerous physiological pathologies
- Typical endogenous production rates are 10-100 pmol/min requiring trace gas detection levels in the range of 10-100 ppbv.

Project Technical Summary

- Overall Project Goal:
  To develop and demonstrate a prototype sensor for multi-gas analysis in exhaled human breath based on a Quantum-Cascade Laser Sensor with Cavity Enhanced Spectroscopy

Multi-Gas QCL-Based Breath Analyzer

- Cavity-enhanced optical cells can provide ~100 m of optical pathlength in 2 cm of physical pathlength
- Each cell capable of ppb-level detection of trace breath radicals (NO, CO), organic biomarkers (pentane, ethane, formaldehyde, acetone, isoprene), and other breath species (ammonia, isotopic CO₂, etc.)
- Configurable array of stacked optical cells arranged along a common breath flow axis should permit rapid, non-invasive assay of basic biological functions with no consumables

Target Gases -1

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formula</th>
<th>Trace Concentration in Breath (ppbv)</th>
<th>Bacterial / Pathological Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric Oxide</td>
<td>NO</td>
<td>6 - 100</td>
<td>Inflammatory / autoimmune responses, e.g., asthma / COPD, Blas, vascular smooth muscle response</td>
</tr>
<tr>
<td>Carbon Monoxide</td>
<td>CO</td>
<td>400 - 3000</td>
<td>Breathing problem, CO poisoning, vascular smooth muscle response, platelet aggregation</td>
</tr>
<tr>
<td>Hydrogen Peroxide</td>
<td>H₂O₂</td>
<td>1 - 5</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Carbon Dioxide</td>
<td>CO₂</td>
<td>4 - 5 x 10⁴</td>
<td>Hypoxia, pulmonary edemaogenicity</td>
</tr>
<tr>
<td>Carbon Dioxide / H₂O₂</td>
<td></td>
<td>4 - 5 x 10⁴</td>
<td>Marker for leukocyte pyrene detection, SII and hyperactivity</td>
</tr>
</tbody>
</table>
**Target Gases - 2**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formula</th>
<th>Trace Concentration in Breath (ppb)</th>
<th>Biological Pathology Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>CH₂O</td>
<td>1000 - 8000</td>
<td>Gaseous tumor</td>
</tr>
<tr>
<td>Methane</td>
<td>CH₄</td>
<td>1000 - 8000</td>
<td>Gaseous tumor</td>
</tr>
<tr>
<td>Ammonia</td>
<td>NH₃</td>
<td>100 - 500</td>
<td>Gaseous tumor, hyperventilation,</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>CH₃COOH</td>
<td>1000 - 5000</td>
<td>Gaseous tumor, diabetes mellitus</td>
</tr>
</tbody>
</table>

**Target Gases - 3**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formula</th>
<th>Trace Concentration in Breath (ppb)</th>
<th>Biological Pathology Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>H₂</td>
<td>10 - 30</td>
<td>Oral infection, hallucination</td>
</tr>
<tr>
<td>Methane</td>
<td>CH₄</td>
<td>10 - 30</td>
<td>Oral infection, hallucination</td>
</tr>
<tr>
<td>Dimethyl ether</td>
<td>CH₃-OCH₃</td>
<td>10 - 30</td>
<td>Oral infection, hallucination</td>
</tr>
<tr>
<td>Propene</td>
<td>C₃H₆</td>
<td>50 - 400</td>
<td>Chorionic synthesis, acute neonatal infections, cancer exposure, hemolytic anemia, respiratory upset monitoring</td>
</tr>
<tr>
<td>Acetone</td>
<td>C₃H₆O</td>
<td>50 - 400</td>
<td>Gaseous trace to measure pulmonary function and cardiac output</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>NO</td>
<td>50 - 400</td>
<td>Gaseous trace to measure pulmonary function</td>
</tr>
</tbody>
</table>

**Key Characteristics of Quantum Cascade Lasers**

- Laser wavelengths cover the entire range from 3.4 to 24 μm determined by layer thickness of same materials
- High power (100 mW cw, 50 mW average, pulsed)
- High spectral purity - single frequency with DBF structure
- Continuous tuning by temperature or current (1-10 cm⁻¹)
- High reliability: low failure rate, long lifetime and robust fabrication
- Capable of near-room temperature operation
  - Pulsed: up to +150°C
  - CW: up to -63°C

**Ultrasensitive absorption spectroscopy techniques**

1. **Multipass cell spectroscopy**
2. **Cavity enhanced spectroscopy**
3. **Cavity ringdown spectroscopy**

**Trace Gas Detection with a Multipass Cell**

**Breath Samples in the Multipass Cell**

Transmitted intensity of pure nitrogen (black) and a breath sample (red) at 50 Torr and laser current (blue)

Absorption of a breath sample from the nose (red) and the mouth (black) at 50 Torr

Detection limit 3 ppb
Design of proposed CES based Gas Analyzer

Close up of 2 QC Lasers Mounted in Optical Cryostat

High-Sensitivity Detection of Large Molecular Weight, Broadband Absorbers

- Perform coarse, two-wavelength estimate of broad absorption feature using two, time-domain-multiplexed QCL's:

- With a balanced ratio detector, expect to achieve $\alpha_{\text{max}} = 10^{-4} - 10^{-5}$

Comparison of Available QCL's to Absorption Features of Trace Volatile Organics in Breath

- Acetone selected as first target

- Will investigate possible ethanol interference

Integrated Project Schedule and Milestones

- Parallel efforts in spectroscopy, optics, and systems development

Program Status

- Program initiated January 2002.
- Rice – Available $\approx$1920.5 cm$^{-1}$ laser adapted to cryogenic mount for cw operation. Short (1 in.) cavity constructed.
- LGR – Initiated design/fabrication of $\approx$1900 cm$^{-1}$ (NO) and 2165 cm$^{-1}$ (CO) mirror sets. Developing design specifications for multi-mirror cavities.
- PSI – Preliminary dual-laser measurements underway for acetone detection at 1180/1200 cm$^{-1}$ using conventional, single-pass absorption to establish baseline detection limits.