Photonic Technologies for Early Detection of Human Disease

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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

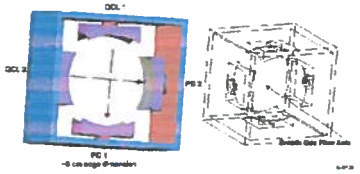
Trace Reactive Gases As Physiological Messengers

- NO production is tied to numerous physiological processes
  - vasorelaxation, inflammation, thrombosis, immunity
  - reduced NO production associated with atherosclerosis and ulcers
  - enhanced NO production associated with asthma, endotoxin shock, diabetes, and edema
- CO production is important in vascular muscle cell physiology and platelet aggregation
- Trace levels of these and other breath species are associated with numerous physiological pathologies
- Typical endogenous production rates are~ 10 pmol/min requiring trace gas detection levels in the range of 1to 10 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 CO_2, 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

Molecule	Formula	Trace Concentration in Breath (ppb)	Biological/Pathology Indication
Nitric Oxide	NO	6 - 100	Inflammatory and immune responses (e.g., asthma, COPD, IBD), vascular smooth muscle response
Carbon Monoxide	CO	400 - 3000	Smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation
Hydrogen Peroxide	H_2O_2	1 - 5	Oxidative stress
Carbon Dioxide	CO_2	$4 - 5 \times 10^7$	Hypoxia, pulmonary diffusing capacity
Carbon Dioxide isotope ratio	$^{13}CO_2/^{12}CO_2$	$4 - 5 \times 10^5$	Marker for Helicobacter pylori infection, GI and hepatic function

Target Gases -2

Molecule	Formula	Trace Concentration in Breath (ppb)	Biological/ Pathology Indication
Pentane	$CH_3(CH_2)_3CH_3$	4 - 20	Lipid peroxidation, oxidative stress associated with inflammatory diseases, immune responses, transplant rejection, breast and lung cancer
Ethane	C_2H_6	3 - 100	Lipid peroxidation and oxidative stress
Formaldehyde	HCHO	1000 - 8000	Cancerous tumors
Methane	CH_4	1000 - 8000	Digestive function, colonic fermentation
Ammonia	NH_3	100 - 500	Hepatic encephalopathy, liver cirrhosis, fasting response
Acetone	CH_3COCH_3	1000 - 5000	Fasting response, diabetes mellitus response, ketosis

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Target Gases -3

Molecule	Formula	Trace Concentration in Breath (ppb)	Biological/ Pathology Indication
Hydrogen Sulfide	H_2S	10 - 30	Oral infection, halitosis
Methyl mercaptan	CH_3SH	10 - 30	Oral infection, halitosis
Dimethyl sulfide	$C2H_3S$	2 - 20	Oral infection, halitosis
Isoprene	$CH_2=C(CH_3)-CH=CH_2$	40 - 400	Cholesterol synthesis, acute myocardial infarction, ozone exposure, hemodialysis response, sleep/wakefulness monitoring
Acetylene	C_2H_2	Additive	Exogenous tracer to measure pulmonary function and cardiac output
Sulfur hexafluoride	SF_6	Additive	Exogenous tracer to measure pulmonary function

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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 DFB 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

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Ultrasensitive absorption spectroscopy techniques

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

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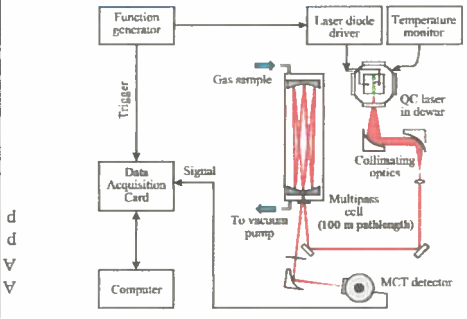
Trace Gas Detection with a Multipass Cell



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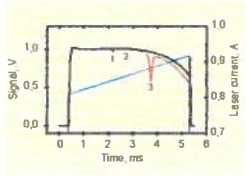
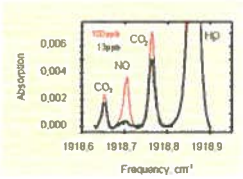
Breath Samples in the Multipass Cell



Transmitted intensity of pure Nitrogen (black) and a breath sample (red) at 50Torr and laser current (blue).
(1) HO @ 1918.860 cm, (2) CO_2@ 1918.76 cm, (3) CO_2@ 1918.585 cm



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

Detection limit 3 ppb

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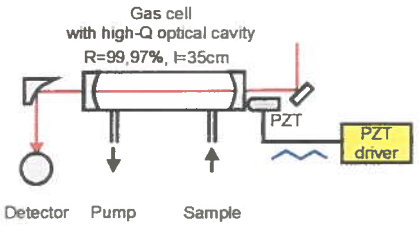
CES Detection of NO



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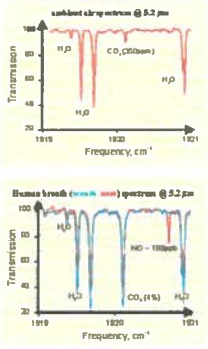
CES Spectra -Breath Samples



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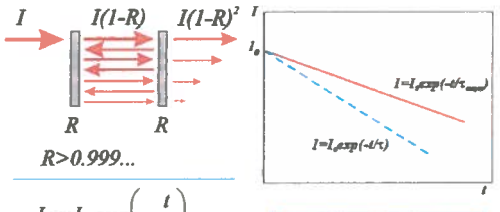
Cavity Ring-Down Spectroscopy



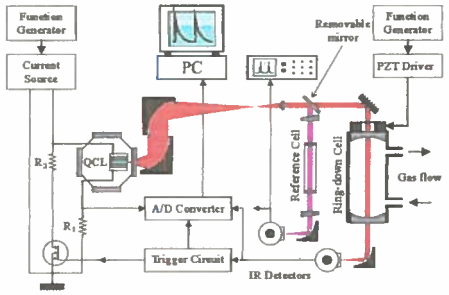
$R>0.999...$

$$I = I_0 \exp\left(-\frac{t}{\tau}\right)$$

$$\tau = \frac{l}{c} \cdot \frac{1}{\alpha l - \ln\sqrt{R_1 R_2}}$$

$$\alpha = \frac{1}{c}\left(\frac{1}{\tau} - \frac{1}{\tau_{empty}}\right)$$

CRDS Gas Sensor



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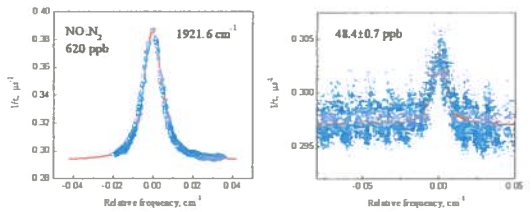
NO absorption, 60 Torr Total Pressure



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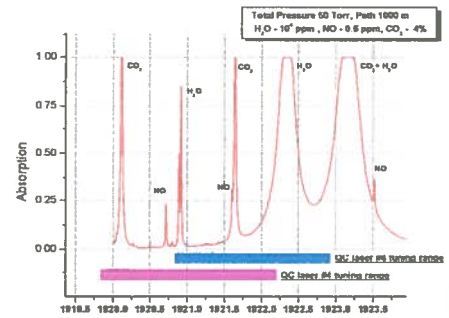
HITRAN simulation of NO spectrum @ 5.2 μm



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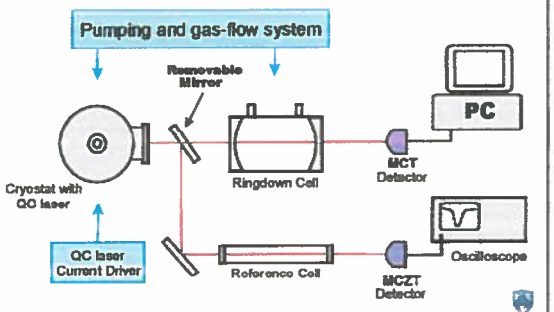
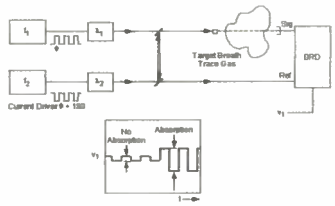
Design of proposed CES based Gas Analyzer



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 $\alpha_{min} = 10^{-4} - 10^{-5}$

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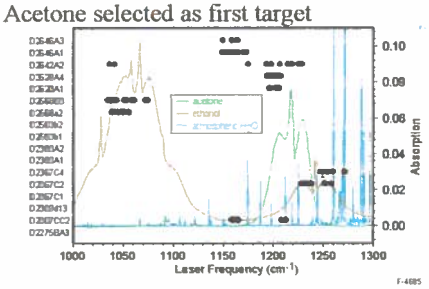
Comparison of Available QCL's to Absorption Features of Trace Volatile Organics in Breath

- Acetone selected as first target

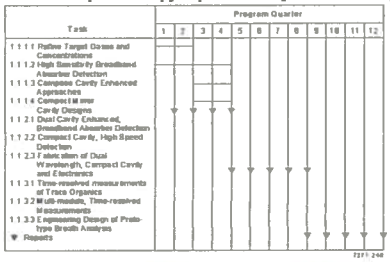
ISI



- Will investigate possible ethanol interference

Integrated Project Schedule and Milestones

- Parallel efforts in spectroscopy, optics, and systems development



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Program Status

- Program initiated January 2002.
- Rice – Available ~1920.5 cm^{-1} laser adapted to cryogenic mount for cw operation. Short (1 in.) cavity constructed.
- LGR – Initiated design/fabrication of ~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.

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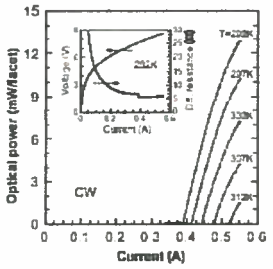
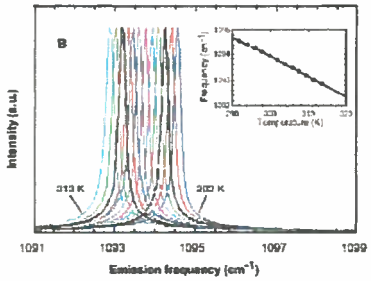
CW Operation of Mid-IR QC Laser at Room Temperature



M. Beck et al. Science Dec. 20, 2001

Temperature Dependence of CW QC Laser Spectra



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